

Neuropsychological Effects of MRI-Detected Brain Lesions After Left Atrial Catheter Ablation for Atrial Fibrillation

Long-Term Results of the MACPAF Study

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Background—MRI-detected brain lesions are common after left atrial catheter ablation for symptomatic atrial fibrillation. The clinical relevance of these acute ischemic lesions is not fully understood, but ablation-related cerebral injury could contribute to cognitive dysfunction.

Methods and Results—In the prospective Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal Atrial Fibrillation (MACPAF) study, serial 3-T brain MRIs and neuropsychological assessment were performed to analyze the rate of ablation-related brain lesions and their effect on cognitive function. Thirty-seven patients with paroxysmal atrial fibrillation (median age, 63.0 [interquartile range, 57–68] years; 41% female; median CHA₂DS₂-VASc score 2 [interquartile range, 1–3]) underwent 41 ablation procedures according to study criteria. None of these patients had overt neurological deficits after ablation. High-resolution diffusion-weighted imaging, performed within 48 hours after ablation, showed that new brain lesions (range, 1–17) were present in 16 (43.2%) patients after 18 (43.9%) left atrial catheter ablation procedures. Follow-up MRI at 6 months (median, 6.5; interquartile range, 6–7) revealed that 7 (12.5%) of the 56 total acute brain lesions after ablation formed a persistent glial scar in 5 (31.3%) patients. Large diffusion-weighted imaging lesions and a corresponding fluid-attenuated inversion recovery lesion 48 hours after ablation predicted lesion persistence on 6-month follow-up. Neither persistent brain lesions nor the ablation procedure itself had a significant effect on attention or executive functions, short-term memory, or verbal and nonverbal learning after 6 months.

Conclusions—Ablation-related acute ischemic brain lesions persist to some extent but do not cause cognitive impairment 6 months after the ablation procedure.

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Key Words: atrial fibrillation ■ catheter ablation ■ cognition ■ magnetic resonance imaging ■ stroke

Left atrial catheter ablation (LACA) of the pulmonary veins is a well-established therapeutic approach to abolish symptomatic paroxysmal or persistent atrial fibrillation (AF) in patients who are refractory to antiarrhythmic medication.^{1,2} However, the ablation procedure generates several potential risks for thromboembolism, such as insertion of thrombogenic catheters and sheaths, left atrial endothelial lesions, systemic activation of platelets and the coagulation system, left atrial diastolic dysfunction, or air emboli via the left atrial sheaths.³ Subsequently, LACA bears a periprocedural stroke risk of ≈0.5% and a similar risk for transient ischemic attacks.³ MRI is likely more sensitive than clinical observation for the detection of ablation-related brain damage.

MRI studies have recently revealed that acute ischemic brain lesions occur in 4% to 41% of patients after ablation,^{3,4} a range that is dependent on the catheter device used for ablation^{5,6} and the MRI technique used for lesion detection (eg, high-resolution diffusion-weighted imaging [hrDWI]).⁷ Frequently, postablation damage manifests itself in the form of silent or subclinical strokes, which do not cause overt neurological deficits but might contribute to neuropsychological impairment⁸ that commonly go unnoticed. However, cognitive deficits have also been reported in patients after cardiac surgery⁹ and in those with persistent AF.^{10,11}

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Although catheter ablation is now a routine procedure in many centers worldwide, the present information on the clinical relevance of MRI-detected brain lesions after ablation has been generated from small case series and thus remains uncertain.^{4,12,13}

We recently reported that, in the prospective Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal Atrial Fibrillation (MACPAF) study, 3-T hrDWI detected acute ischemic lesions in a sample of 37 LACA patients (41%) 48 hours after LACA. However, no significant cognitive decline was observed within 48 hours after ablation.⁷

Here, we report the long-term follow-up data from the MACPAF study. To assess the incidence, persistence, and clinical effect of ablation-related brain lesions, which was the predefined secondary objective of the study, we performed serial brain MRI and neuropsychological testing 6 months after LACA.

We attempted to answer the following questions: (1) How many acute brain lesions postablation will form glial scars after 6 months? (2) Were these brain lesions associated with cognitive decline 6 months after ablation? (3) Does the ablation procedure itself cause neurocognitive impairment?

Methods

Study Design

The MACPAF study design has been described previously.^{14,15} Briefly, MACPAF compared the efficacy and safety of the HD Mesh Ablator catheter (C.R. Bard, Inc) and the Arctic Front catheter (Medtronic, Inc) in patients with symptomatic paroxysmal AF. MACPAF was terminated prematurely because the first interim analysis revealed an insufficient efficacy of the HD Mesh Ablator on the primary outcome measure (exit block in all pulmonary veins).¹⁶ Overall, 37 patients underwent 41 ablation procedures according to the study criteria. Four patients with symptomatic AF episodes after ablation underwent a second LACA using the Arctic Front catheter. MRI using a 3-T device (Tim Trio; Siemens AG, Erlangen, Germany) and neurological examinations were performed within 48 hours before and after LACA and again on follow-up 6 months later. Neuropsychological assessment was scheduled before LACA, within 48 hours after ablation, and after 6 months.

MR Imaging, Neurological Examination, and Neuropsychological Examination

The MRI protocol has been described in detail previously.^{7,14} MRI sequences were defined as follows: T2*—repetition time (TR), 620 ms; echo time (TE), 20 ms; field of view, 220 mm; matrix, 256×192; slice thickness, 5 mm; hrDWI—TR, 7600 ms; TE, 93 ms; field of view, 230 mm; matrix size, 192×192; slice thickness, 2.5 mm; diffusion gradients in 6 directions of $b=1000$ s/mm², trace-weighted images, and apparent diffusion coefficient maps were post-processed; fluid-attenuated inversion recovery (FLAIR)—TR, 8000 ms; TE, 100 ms; inversion time, 2370 ms; field of view, 220 mm; matrix size, 256×232; slice thickness, 5 mm with 0.5-mm interslice gap; time-of-flight angiography—TR, 22 ms; TE, 3.86 ms; field of view, 200 mm; matrix size, 384×218; slice thickness, 0.65 mm. To ensure similar image positioning in the Figure, we used SPM8 (Wellcome Department of Imaging Neuroscience, University College London, United Kingdom) running under MATLAB (Mathworks Inc, Natick, MA). We coregistered and spatially normalized imaging data before and after ablation by using DWI B0 data as the reference category. The Wahlund score was used to quantify the extent of pre-existing white matter lesions.¹⁷ Acute brain lesions were defined as restricted diffusion signal according to hrDWI and confirmed by coefficient mapping. The volume of the DWI lesions after ablation was

calculated, and the axial diameter was categorized. Persistent brain lesions were defined as corresponding FLAIR lesions after 6 months. MRIs were interpreted by a board-certified neuroradiologist (J.B.F.).

Neurological deficits were assessed using the National Institutes of Health Stroke Scale¹⁸ and the modified Rankin Scale.¹⁹ Neuropsychological assessment was blinded to MRI results and catheter device. The following inventories were used for neuropsychological evaluations: trail-making test A and B, stroop test, category and letter fluency test, substest 3 from the German Leistungsprüfsystem (LPS 50, comparable with Raven's progressive matrices), a standardized German version of the Rey auditory verbal learning test, digit-span forward and backward test from the Wechsler memory scale—Revised, and the German Mehrfachwahl-Wortschatz-Intelligenztest (MWT-A test, comparable with the American National Adult Reading test), as well as the Rey-Osterrieth complex figure test.¹⁴ Parallel test forms of the Rey auditory verbal learning test, LPS, and Rey-Osterrieth complex figure test were used.

Ablation Procedure

Ablation procedures using the Arctic Front or the HD Mesh Ablator catheter have been described in detail previously.¹⁶ All patients underwent transesophageal echocardiography within 24 hours before LACA to rule out cardiac thrombi. Ablation procedures were performed under sedation (using propofol and midazolam) and analgesia (using fentanyl) but without assisted ventilation. Before transseptal puncture, a heparin bolus of 2,000 IU was administered, followed by further heparin boli directly after transseptal puncture and before insertion of any ablation catheter to maintain an activated clotting time (ACT) of >300 seconds. The ACT was measured every 20 minutes, and the transseptal sheaths were flushed continuously with saline (200 mL/h) to avoid embolization. Periprocedural cardioversion was performed in cases of persisting AF after ablation of all pulmonary veins. All patients were monitored after the procedure by using a telemetric ECG system for ≥48 hours. Oral anticoagulation (vitamin K antagonists) was stopped 7 days before ablation and replaced by low-molecular-weight heparin if the international normalized ratio was <2. Anticoagulation with low-molecular-weight heparin was started on the day of LACA and followed by oral anticoagulation. Overall, 85% of all patients received oral anticoagulation for ≥6 months.

Statistical Analysis

Absolute and relative frequencies were reported for categorical variables. As a result of small sample sizes, normal distribution of continuous variables cannot be assumed. Therefore, medians and quartiles were calculated for all other variables. Fisher exact tests were used to compare proportions of dichotomous outcomes between independent groups or to test the independence of 2 dichotomous variables within a population. Mann–Whitney tests were used for group-specific location parameters, assuming equal distributions in the 2 treatment groups for ordinal outcome variables. Comparing the results of neuropsychological testing in all study patients before ablation and 6 months after ablation, we used the Wilcoxon signed-rank test. By comparing neuropsychological results in patients with or without acute/persisting brain lesions across groups, differences in individual differences of neuropsychological test results before and after ablation were computed (Tables I and II in the online-only Data Supplement for details). The resulting variables were compared using the Mann–Whitney test. Because the required sample size calculation for the MACPAF study was not met, all statistical analyses have to be regarded as exploratory. $P<0.05$ indicate possible associations but were not adjusted for multiple testing.

Results

Patient Characteristics and MRI Findings After Ablation

Thirty-seven patients (median age, 63.0 [interquartile range {IQR}, 57–68] years; 41% female; median preadmission CHA₂DS₂VASc score, 2 [IQR, 1–3]) underwent 41 ablation

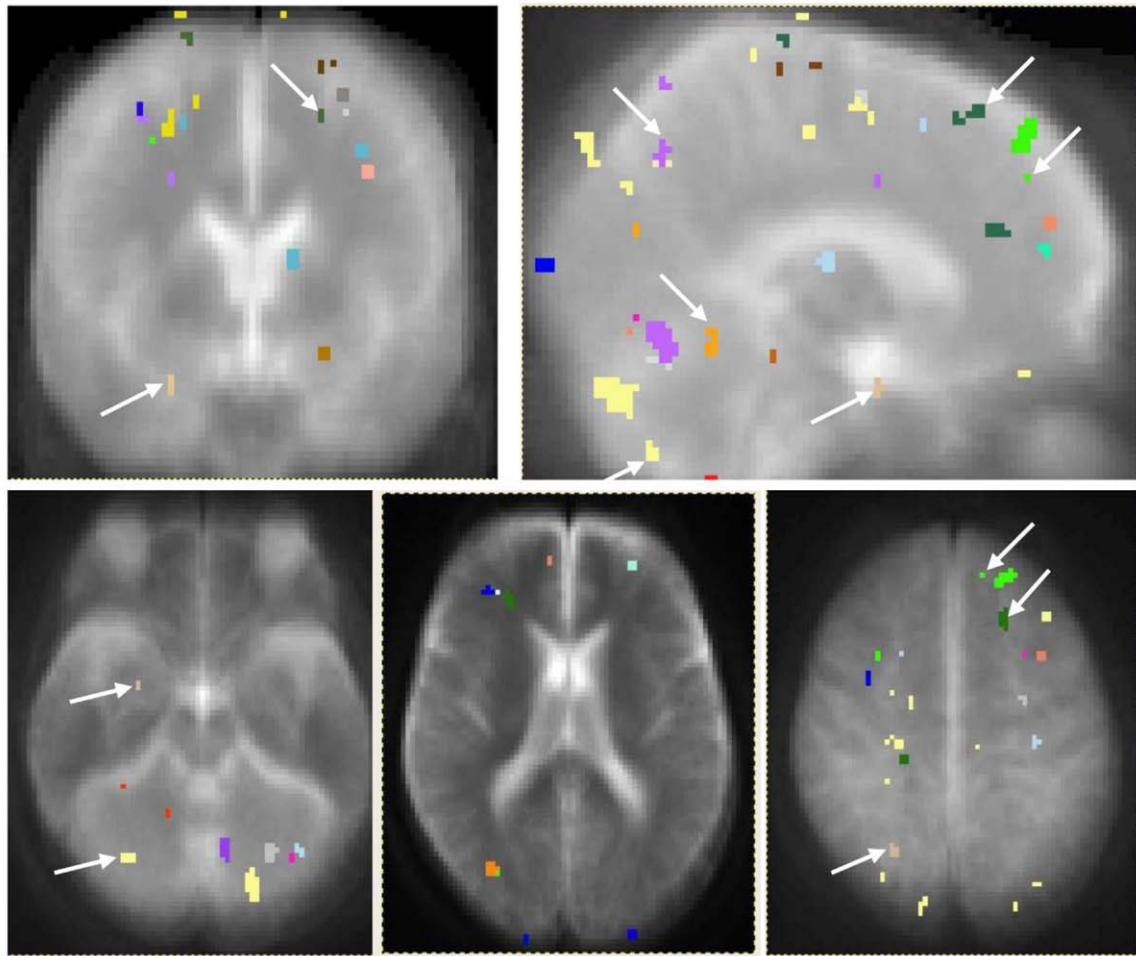


Figure. Spatial distribution of high-resolution diffusion-weighted imaging–detected brain lesions within 48 hours after ablation on the coregistered and spatially normalized diffusion-weighted imaging B0 MR images. Different colors were chosen for each patient (n=16). Persisting brain lesions on fluid-attenuated inversion recovery imaging after 6 months are indicated by arrows.

procedures using either the Arctic Front (n=26) or HD Mesh Ablator catheter (n=15). None of the patients reported neurological symptoms, and neurological examinations did not reveal neurological deficits after the ablation procedure. Within 48 hours after ablation, a total of 56 acute DWI lesions were detected. These DWI lesions were found in 16 (43.2%) patients (median age, 64.0 [IQR, 58–68] years; 31% female; median CHA₂DS₂-VASc score, 2 [IQR, 1–3]; Table 1). In other words, DWI lesions were detected after 18 (43.9%) of 41 ablation procedures. Neither age ($P=0.58$), sex ($P=0.52$), CHA₂DS₂-VASc score ($P=0.48$), catheter device ($P=0.11$), preablation Wahlund score ($P=0.34$), preablation left atrial volume ($P=0.18$), nor periprocedural ACT levels ($P=0.83$) had a significant effect on the appearance of DWI lesions after ablation.

As depicted in the Figure and Table 2, DWI lesions after ablation were distributed throughout the brain and were generally small. Overall, 38 (67.8%) of the 56 DWI lesions occurred in the cortex. Up to 17 lesions were detected per patient (median, 2.0 [IQR, 1.0–3.8]). We observed no conspicuous features in the patient with 17 acute brain lesions (CHA₂DS₂-VaSc score, 4; ACT levels were 259–313 seconds; no periprocedural AF). The median volume of the 56 DWI lesions was 11.8 mm³ (IQR,

6.4–25.4 mm³; range, 2.6–150.1 mm³). Fifteen (26.8%) DWI lesions were also present on corresponding FLAIR images within 48 hours after ablation.

MRI Findings 6 Months After Ablation

Follow-up MRI was scheduled 6 months after LACA and performed in all patients (median, 6.5 [IQR, 6–7] months). According to our preliminary data evaluation, 18 (48.6%) of 37 study patients had documented AF between day 90 and day 180 after ablation. None of the patients experienced territorial ischemia during follow-up. There were no acute DWI lesions after 6 months. Seven (12.5%) of the 56 DWI lesions after ablation were visible on corresponding FLAIR images in 5 (31.3%) patients. Baseline characteristics, ablation-related factors (Table 1), and lesion characteristics (Table 2) were compared in patients with or without persisting brain lesions. Neither age ($P>0.995$), sex ($P>0.995$), cardiovascular risk factors, medication preablation, nor ablation-related factors such as periprocedural ACT levels, catheter device, or AF episodes during LACA had a significant effect on persistence of brain lesions. However, a corresponding FLAIR lesion immediately after ablation predicted the persistence of brain lesions ($P<0.001$). In addition, DWI lesion

Table 1. Baseline Characteristics of Patients With DWI-Detected Brain Lesions After Ablation According to Persistence of Brain Lesions 6 Months After Ablation

	MRI Postablation			MRI 6 mo Postablation		
	No Acute Brain Lesions (n=21)	Acute Brain Lesion (n=16)*	P Value†	No Persisting Brain Lesion (n=11)	Persisting Brain Lesion (n=5)	P Value†
Age, y, median (IQR)	63 (56–69)	64 (58–68)	0.826	63 (60–67)	62 (52–71)	>0.995
Female sex, n (%)	10 (47.6)	5 (31.3)	0.500	3 (27.3)	2 (40.0)	>0.995
CHA ₂ DS ₂ VASc, median (IQR)	2 (1–3)	2 (1–3)	0.887	1 (1–3)	2 (1.5–3)	0.513
Cardiovascular risk factors, n (%)						
Previous stroke	2 (9.5)	1 (6.3)	>0.995	0 (0.0)	1 (20.0)	0.313
Hypertension	11 (52.4)	9 (56.3)	>0.995	5 (45.5)	4 (80.0)	0.308
Diabetes mellitus	2 (9.5)	3 (18.8)	0.634	2 (18.2)	1 (20.0)	>0.995
Heart failure	0 (0)	1 (6.3)	0.432	1 (9.1)	0 (0.0)	>0.995
Coronary artery disease	5 (23.8)	3 (18.8)	>0.995	2 (18.2)	1 (20.0)	>0.995
Obesity	6 (28.6)	9 (56.3)	0.107	7 (63.6)	2 (40.0)	0.596
Hyperlipoproteinemia	12 (57.1)	8 (50.0)	0.746	5 (45.5)	3 (60.0)	>0.995
Preablation MRI findings, n (%)						
Previous stroke	2 (9.5)	1 (6.3)	>0.995	1 (9.1)	0 (0.0)	>0.995
Wahlund score, median (IQR)	2.0 (0–4)	2.0 (0–4)	0.539	1.0 (0–4)	4.0 (0–5)	0.788
LACA catheter						
HD Mesh Ablator	10 (47.6)	4 (25.0)	0.191	4 (36.4)	0 (0.0)	0.245
Arctic Front	11 (52.4)	12 (75.0)		7 (63.6)	5 (100.0)	
AF episodes during LACA	8 (38.1)	10 (62.5)	0.331	7 (63.6)	3 (60.0)	>0.995
Cardioversion during LACA	3 (14.3)	4 (25.0)	0.437	3 (27.3)	1 (20.0)	>0.995
Medication during ablation						
ACT level during ablation, median (IQR), s	293 (259–329)	294 (270–308)	0.844	298 (263–310)	292 (276–308)	>0.995
ACT intermittent <200 s, n (%)	2 (9.5)	1 (6.3)	>0.995	1 (9.1)	0 (0.0)	>0.995
ACT intermittent <250 s, n (%)	7 (33.3)	6 (37.5)	>0.995	5 (45.5)	1 (20.0)	0.588
ACT intermittent <300 s, n (%)	19 (90.5)	15 (93.8)	>0.995	10 (90.9)	5 (100.0)	>0.995
Medication prior ablation						
Antiplatelets	14 (66.7)	7 (43.8)	0.196	6 (54.5)	1 (20.0)	0.308
Statins	8 (38.1)	8 (50.0)	>0.995	5 (45.5)	3 (60.0)	>0.995

ACT indicates activated clotting time; AF, atrial fibrillation; DWI, diffusion-weighted imaging; IQR, interquartile range; and LACA, left atrial catheter ablation.

*Ischemic lesions were detected in 15 patients after their first ablation and in 1 of 4 study patients only after the second ablation procedure.

†P values based on Fisher exact test or Mann-Whitney test, respectively.

volume ($P=0.06$) and axial lesion diameter ($P=0.07$) tended to inversely associate with lesion persistence. All persistent lesions were found in patients who underwent LACA with the Arctic Front device. However, lesion volumes, diameters, and distributions did not differ according to catheter device (Table 3).

Neuropsychological Sequelae of Periprocedural Brain Lesions

None of the patients reported neurological or cognitive deficits during follow-up. β -Blockers were discontinued in 2 patients and additively given in 2 patients within 6 months after ablation, indicating that 89% of all included patients were taking β -blockers during follow-up. Serial neuropsychological testing was complete in 35 (94.6%) of the 37 patients and after 39 (95.1%) of the 41 ablation procedures. One patient refused serial neuropsychological testing because of difficulties in understanding and speaking

German and English. Another patient refused neuropsychological testing 6 months after the second ablation procedure. None of the patients complained of cognitive dysfunction on follow-up. Comparisons of interpersonal results before and after ablation (median, 6.5 [IQR, 6–7] months) revealed that no significant changes in attention span, executive functions (assessed by the trail-making test, category and letter fluency test, and digit-span backward test), short-term memory (forward digit-span task), or verbal and nonverbal learning (Rey-Osterrieth complex figure test and the Rey auditory verbal learning test) were present (Table 4). Reasoning performance (assessed by the LPS 50) significantly improved ($P=0.002$), as well as 1 domain of attention and executive functions (assessed by the color-word interference test; $P=0.005$). Neuropsychological differences did not differentially associate with persistent brain lesions (Table 5). Furthermore, recurrent AF within 3 and 6 months after ablation had no effect on cognitive performance.

Table 2. Characteristics of 56 MRI-Detected Brain Lesions After Ablation According to Persistence 6 Months After Ablation

MRI Postablation	MRI 6 mo Postablation		P Value*
	No Persisting Brain Lesion (n=49)	Persisting Brain Lesion (n=7)	
DWI lesion size, median (IQR), mm ³	11.2 (6.0–19.4)	25.7 (9.5–40.7)	0.074
DWI lesion size, n (%)			
<20 mm ³	38 (77.6)	2 (28.6)	
≥20 and <50 mm ³	7 (14.3)	4 (57.1)	
≥ 50 and <100 mm ³	1 (2.0)	0	
≥100 mm ³	3 (6.1)	1 (14.3)	
Axial DWI diameter, median (IQR), mm ³	9.0 (4.8–15.5)	20.5 (7.6–32.6)	0.062
Axial DWI diameter, n (%)			
<3 mm	19 (38.8)	2 (28.6)	
≥3 and <6 mm	27 (55.1)	3 (42.9)	
≥6 mm	3 (6.1)	2 (28.6)	
Affected vessel territory, n (%)			0.067
Arteria cerebri media	15 (30.6)	5 (71.4)	
Arteria cerebri anterior	18 (36.7)	0	
Arteria cerebri posterior	9 (18.4)	2 (28.6)	
Vertebral/basilar artery	7 (14.3)	0 (0.0)	
Left hemisphere affected, n (%)	23 (46.9)	3 (42.9)	0.700
FLAIR lesion postablation, n (%)	9 (18.4)	6 (85.7)	0.001

DWI indicates diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; and IQR, interquartile range.

*P values based on Fisher exact test or Mann–Whitney test, respectively.

Discussion

Subclinical ischemic brain lesions are frequently present in DWI acutely after LACA⁷ and invasive cardiovascular procedures, such as diagnostic coronary angiography,^{20,21} patent foramen ovale occlusion,²² percutaneous transfemoral aortic valve implantation,²³ and cardiac surgery.²⁴ Between 8% and 18% of all LACA patients show DWI lesions using 1.5-T imaging.^{3,4} hrDWI, however, is capable of identifying

Table 3. Characteristics of 56 MRI-Detected Brain Lesions After Ablation According to Catheter Devices

	HD Mesh Ablator	Arctic Front	P Value*
	(n=13)	(n=43)	
DWI lesion size, median (IQR), mm ³	10.5 (6–26)	15.0 (9–29)	0.315
DWI axial diameter, median (IQR), mm	12.0 (7–23)	8.4 (5–20)	0.306
Affected vessel territory, n (%)			
Arteria cerebri media	3 (15.0)	17 (39.5)	0.339
Arteria cerebri anterior	3 (23.1)	15 (34.9)	0.514
Arteria cerebri posterior	5 (38.5)	6 (14.0)	0.104
Vertebral/basilar artery	2 (15.4)	5 (11.6)	0.658
Left hemisphere affected, n (%)	8 (61.5)	19 (44.2)	0.349
Persisting brain lesions	0	7 (26.5)	0.182

DWI indicates diffusion-weighted imaging; and IQR, interquartile range.

*P values based on Fisher exact test or Mann–Whitney test, respectively.

upward of twice as many (cortical) lesions as standard DWI.¹² Accordingly, we found ischemic brain lesions in 41% of all MACPAF patients who underwent hrDWI within 48 hours of LACA. These silent lesions might contribute to neuropsychological deficits and memory impairment,⁸ as well as epileptic seizures,²⁵ but conclusive data for patients undergoing LACA are lacking.

We recently reported that no significant cognitive decline was apparent 48 hours after ablation, irrespective of the presence of acute brain lesions.⁷ One case–control study, with 23 patients, found that verbal memory scores declined 3 months after LACA²⁶ even in patients without MRI-detected cerebral injury after ablation. Although verbal memory scores were indicative of cognitive decline, this represents only 1 dimension of neuropsychological testing. Furthermore, there was no correlation between cognitive decline and MRI-detected acute brain lesions after ablation. The authors concluded that LACA might have caused minimal ischemia or hypoxia in the hippocampus, temporal, or frontal lobe.²⁶ This finding has raised concerns among treating physicians and patients with AF. Yet, certain limitations of this case series do not allow substantial conclusions.²⁷ In contrast to Schwarz et al,²⁶ we observed no significant alteration in attention and executive functions, short-term memory, or learning 6 months after LACA (Tables 4 and 5). Our results indicate that neither persistent brain lesions after ablation nor the ablation procedure itself had a significant effect on cognitive function after 6 months. Furthermore, recurrent AF had no effect on cognitive performance. However, deficits that affect individual skills are beyond the scope of standard test procedures. It remains to be established whether LACA can reduce AF-related cognitive decline^{10,11} by restoring sinus rhythm, as suggested by a retrospective matched-pair analysis reporting similar dementia rates across patients with AF who underwent successful LACA and patients without AF.²⁸

MACPAF is the first prospective trial with complete long-term follow-up MRI data. Two recent studies using 1.5-T MRI have reported that ≈6% of all brain lesions persisted (n=14 patients) after a median of 3 months¹³ and that no lesions persisted (n=9 patients) after a median of 21 months.⁴ Our 3-T data show that 13% of all DWI lesions 48 hours after ablation were visible as glial scars after 6 months. Lesions with smaller DWI volumes were less likely to cause glial scars, as similarly reported by Deneke et al.¹³ As expected, a corresponding FLAIR lesion immediately after ablation predicted lesion persistence on FLAIR images after 6 months (Table 2). It is important to note that slice thicknesses on postablation hrDWI (2.5 mm) and follow-up FLAIR images (5 mm) varied and probably caused the low rate of lesion persistence. Nevertheless, DWI lesions might be fully reversible as shown in patients with transient ischemic attack without persisting brain lesion on follow-up MRI.²⁹

Although prevention of ablation-related complications is of clinical importance, we aimed to identify factors contributing to occurrence or persistence of ablation-related brain lesions. As similarly described for patients with acute DWI lesions immediately after ablation,⁷ neither age, sex, CHA₂DS₂VASc score, catheter device, preablation Wahlund score, left atrial volume, nor periprocedural ACT levels associated with lesion persistence 6 months after ablation (Tables 1 and 2). Despite

Table 4. Neuropsychological Assessment Before Ablation and 6 Months After Ablation According to the Presence of DWI Lesions

	LACA-Procedures (n=39/41)			DWI Lesion Postablation (n=16/18)			No DWI Lesion Postablation (n=23)			
	Pre-LACA	6 mo	P Value*	Pre-LACA	6 mo	P Value*	Pre-LACA	6 mo	P Value*	P Value†
Attention and executive functions										
Trail-making test A, s	38 (30–45)	31 (26–47)	0.932	42 (28–47)	31 (28–35)	0.213	33 (30–43)	38 (26–51)	0.467	0.141
Trail-making test B, s	83 (69–104)	78 (61–110)	0.233	81 (70–134)	81 (62–110)	0.184	88 (65–97)	69 (61–110)	0.692	0.493
Color-word interference test, s	153 (139–173)	130 (108–165)	0.005	158 (142–182)	136 (113–167)	0.058	149 (118–166)	129 (107–169)	0.060	0.217
Category fluency, n	25 (19–30)	28 (23–30)	0.057	24 (20–30)	28 (24–32)	0.168	26 (18–30)	26 (22–30)	0.271	0.367
Letter fluency, n	17 (11–19)	17 (12–22)	0.634	13 (10–19)	18 (11–23)	0.225	18 (13–21)	16 (12–19)	0.626	0.235
Digit-span backward, points	6 (5–8)	7 (6–9)	0.338	6 (5–8)	6 (5–8)	0.756	7 (5–8)	8 (6–9)	0.146	0.181
Short-term memory										
Digit-span forward, points	8 (7–10)	8 (8–10)	0.509	8 (6–10)	9 (8–10)	0.521	8 (7–10)	8 (8–9)	0.806	0.704
Learning (verbal and nonverbal)										
RAVLT,‡ n	8 (7–10)	9 (8–11)	0.217	7 (6–10)	9 (7–11)	0.353	8 (7–11)	9 (8–11)	0.422	0.797
ROC figure,§ points	26 (22–30)	27 (25–30)	0.195	25 (20–29)	27 (24–29)	0.234	27 (24–29)	26 (25–30)	0.658	0.358
Reasoning										
LPS 50, points	22 (18–24)	25 (20–26)	0.002	20 (17–25)	24 (17–26)	0.111	22 (20–24)	25 (21–26)	0.006	0.696

Values are expressed as median (IQR). DWI indicates diffusion-weighted imaging; IQR, interquartile range; LACA, left atrial catheter ablation; RAVLT, rey auditory verbal learning test; and ROC figure, Rey-Osterrieth complex figure.

*P values based on the Wilcoxon signed-rank test.

†P values based on the Mann-Whitney test comparing the computed individual difference in neuropsychological test results before ablation and 6 mo after ablation across groups: the computed individual differences are available online (Table I in the online-only Data Supplement).

‡Rey auditory verbal learning test (German Version); delayed recall (A7).

§Rey-Osterrieth complex figure; immediate recall.

||Subtest 3 from the German Leistungsprüfungssystem (LPS).

the fact that we did not observe any difference in lesion volume, size, or distribution of lesions between catheters (Table 3), all persistent brain lesions occurred in the Arctic

Front patients, likely because of the larger size of this group compared with the HD Mesh Ablator group. However, the Arctic Front ablation system has been reported to be more

Table 5. Neuropsychological Assessment Before Ablation and 6 Months After Ablation in Patients With MRI-Detected Acute Brain Lesions After Ablation According to Persistence of Brain Lesions

	No Persisting Brain Lesion (n=33/34)			Persisting Brain Lesion(s) (n=6/7)			
	Pre-LACA	6 mo	P Value*	Pre-LACA	6 mo	P Value*	P Value†
Attention and executive functions							
Trail-making test A, s	40 (31–46)	31 (26–49)	0.578	26 (19–38)	38 (26–51)	0.219	0.134
Trail-making test B, s	88 (70–108)	72 (61–110)	0.247	71 (60–104)	69 (61–110)	0.625	0.499
Color-word-interference test, s	157 (135–178)	130 (106–171)	0.014	146 (141–158)	129 (107–169)	0.313	0.886
Category fluency, n	25 (19–30)	28 (23–30)	0.031	29 (22–34)	26 (22–30)	>0.995	0.295
Letter fluency, n	17 (11–19)	17 (12–22)	0.597	18 (11–26)	16 (12–19)	>0.995	0.761
Digit-span backward, points	7 (6–9)	8 (6–9)	0.199	6 (5–7)	8 (6–9)	0.500	0.221
Short-term memory							
Digit-span forward, points	8 (7–10)	8 (8–10)	0.465	9 (5–9)	8 (8–9)	>0.995	0.742
Learning (verbal and nonverbal)							
RAVLT,‡ n	8 (6–11)	9 (8–11)	0.509	7 (7–10)	9 (8–11)	0.188	0.207
ROC figure,§ points	27 (21–30)	27 (25–30)	0.303	24 (22–26)	26 (25–30)	0.406	0.630
Reasoning							
LPS 50, points	22 (19–24)	25 (21–26)	0.001	20 (16–22)	25 (21–26)	0.813	0.334

Values are expressed as median (IQR). IQR indicates interquartile range; LACA, left atrial catheter ablation; RAVLT, rey auditory verbal learning test; and ROC figure, Rey-Osterrieth complex figure.

*P values based on the Wilcoxon signed-rank test.

†P values based on the Mann-Whitney test: the computed individual differences are available online (Table II in the online-only Data Supplement).

‡Rey auditory verbal learning test (German Version); delayed recall (A7).

§Rey-Osterrieth complex figure; immediate recall.

||Subtest 3 from the German Leistungsprüfungssystem (LPS).

prone to air embolism,²⁹ meaning that the composition of cerebral thrombi might depend on the catheter device. However, our MRI data do not enable us to verify that issue.

The prospective design of MACPAF, standardization, blinded assessment of neuropsychological testing, and the nearly complete midterm follow-up strengthen our results and address relevant clinical questions. To the best of our knowledge, MACPAF is the largest study to date that has examined possible associations between neuropsychological performance and MRI lesion persistence after LACA. The investigator-initiated MACPAF study has several limitations. First, and of major importance, because of early termination of the study, the number of study patients was limited. Therefore, we were unable to correct for multiple testing. Second, 2 patients did not undergo serial neuropsychological testing. Third, there was no control group of patients with AF not undergoing LACA. Fourth, the single-center design limits the ability to generalize our results.

Conclusions

Despite widespread use of catheter ablation for symptomatic AF, little is known about possible cognitive side effects of procedure-related brain ischemia. Serial high-sensitivity 3-T brain MRI revealed a considerably high incidence of subclinical strokes immediately after ablation, but the vast majority of these lesions had not formed a detectable glial scar on 6-month follow-up. No cognitive decline was evident in LACA patients during midterm follow-up. The same held true for patients with persisting brain lesions 6 months after the procedure. Nevertheless, prevention of procedure-related cerebral injury is vital and should be addressed in future trials using serial brain MRI.

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References

1. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes N, Page RL, Ezekowitz MD, Slotwimer DJ, Jackman WM, Stevenson WG, Tracy CM, Fuster V, Rydén LE, Cannom DS, Le Heuzey J-Y, Crijns HJ, Olsson SB, Prystowsky EN, Halperin JL, Tamargo JL, Kay GN, Jacobs AK, Anderson JL, Albert N, Hochman JS, Buller CE, Kushner FG, Creager MA, Ohman EM, Ettinger SM, Guyton RA, Tarkington LG, Yancy CW. ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation. *Circulation*. 2011;123:104–123.
2. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Vardas P, Al-Attar N, Alfieri O, Angelini A, Blömstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbüchel H, Heldal M, Kristensen SD, Le Heuzey J-Y, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Rutten FH, Schotten U, Van Gelder IC, Verheugt FWA. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. *Europace*. 2012;14:1385–1413.
3. Haeusler KG, Kirchhof P, Endres M. Left atrial catheter ablation and ischemic stroke. *Stroke*. 2012;43:265–270.
4. Rillig A, Meyerfeldt U, Tilz RR, Talazko J, Arya A, Zvereva V, Birkemeyer R, Miljak T, Hajredini B, Wohlmuth P, Fink U, Jung W. Incidence and long-term follow-up of silent cerebral lesions after pulmonary vein isolation using a remote robotic navigation system as compared with manual ablation. *Circ Arrhythm Electrophysiol*. 2012;5:15–21.
5. Herrera-Siklody C, Deneke T, Hocini M, Lehrmann H, Shin DI, Miyazaki S, Henschke S, Fluegel P, Schiebeling-Römer J, Bansmann PM, Bourdias T, Dousset V, Haissaguerre M, Arentz T. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. *J Am Coll Cardiol*. 2011;58:681–688.
6. Gaita F, Leclercq JF, Schumacher B, Scaglione M, Toso E, Halimi F, Schade A, Froehner S, Ziegler V, Sergi D, Cesarani F, Blandino A. Incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation may change according to technology used: comparison of irrigated radiofrequency, multipolar nonirrigated catheter and cryoballoon. *J Cardiovasc Electrophysiol*. 2011;22:961–968.
7. Haeusler KG, Koch L, Herm J, Kopp UA, Heuschmann PU, Endres M, Schultheiss HP, Schirdewan A, Fiebach JB. 3 Tesla MRI-detected brain lesions after pulmonary vein isolation for atrial fibrillation: results of the MACPAF study. *J Cardiovasc Electrophysiol*. 2013;24:14–21.
8. DeBette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666.
9. Borger MA, Ivanov J, Weisel RD, Rao V, Peniston CM. Stroke during coronary bypass surgery: principal role of cerebral macroemboli. *J Thorac Cardiovasc*. 2001;19:627–632.
10. Knecht S, Oelschläger C, Duning T, Lohmann H, Albers J, Stehling C, Heindel W, Breithardt G, Berger K, Ringelstein EB, Kirchhof P, Wersching H. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J*. 2008;29:2125–2132.
11. Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, Yusuf S. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *CMAJ*. 2012;184:E329–E336.
12. Benamer K, Bykowski JL, Luby M, Warach S, Latour LL. Higher prevalence of cortical lesions observed in patients with acute stroke using high-resolution diffusion-weighted imaging. *AJNR Am J Neuroradiol*. 2006;27:1987–1989.
13. Deneke T, Shin DI, Balta O, Bünz K, Fassbender F, Mügge A, Anders H, Horlitz M, Päsler M, Karthikapallil S, Arentz T, Beyer D, Bansmann M. Postablation asymptomatic cerebral lesions: long-term follow-up using magnetic resonance imaging. *Heart Rhythm*. 2011;8:1705–1711.
14. Haeusler KG, Koch L, Ueberreiter J, Endres M, Schultheiss HP, Heuschmann PU, Schirdewan A, Fiebach JB. Stroke risk associated with balloon based catheter ablation for atrial fibrillation: rationale and design of the MACPAF Study. *BMC Neurol*. 2010;10:63.
15. Haeusler KG, Koch L, Ueberreiter J, Coban N, Safak E, Kunze C, Villringer K, Endres M, Schultheiss HP, Fiebach JB, Schirdewan A. Safety and reliability of the insertable Reveal XT recorder in patients undergoing 3 Tesla brain magnetic resonance imaging. *Heart Rhythm*. 2011;8:373–376.
16. Koch L, Haeusler KG, Herm J, Safak E, Fischer R, Malzahn U, Wernecke T, Heuschmann PU, Endres M, Fiebach JB, Schultheiss HP, Schirdewan A. Mesh ablator vs. cryoballoon pulmonary vein ablation of symptomatic paroxysmal atrial fibrillation: results of the MACPAF study. *Europace*. 2012;14:1441–1449.
17. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, Wallin A, Ader H, Leys D, Pantoni L, Pasquier F, Erkinjuntti T, Scheltens P; European Task Force on Age-Related White Matter Changes. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318–1322.
18. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864–870.
19. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607.
20. Büsing KA, Schulte-Sasse C, Flüchter S, Süselbeck T, Haase KK, Neff W, Hirsch JG, Borggrefe M, Düber C. Cerebral infarction: incidence and risk factors after diagnostic and interventional cardiac catheterization—prospective evaluation at diffusion-weighted MR imaging. *Radiology*. 2005;235:177–183.

21. Kim IC, Hur SH, Park NH, Jun DH, Cho YK, Nam CW, Kim H, Han SW, Choi SY, Kim YN, Kim KB. Incidence and predictors of silent embolic cerebral infarction following diagnostic coronary angiography. *Int J Cardiol*. 2011;148:179–182.
22. Dorenbeck U, Simon B, Skowasch D, Stüsser C, Gockel A, Schild HH, Urbach H, Bauriedel G. Cerebral embolism with interventional closure of symptomatic patent foramen ovale: an MRI-based study using diffusion-weighted imaging. *Eur J Neurol*. 2007;14:451–454.
23. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation*. 2010;121:870–878.
24. Jeon SB, Lee JW, Kim SJ, Chung CH, Kwon SU, Choi CG, Choo SJ, Nah HW, Kim JS, Kang DW. New cerebral lesions on T2*-weighted gradient-echo imaging after cardiac valve surgery. *Cerebrovasc Dis*. 2010;30:194–199.
25. Hiraga A, Ito S, Hayakawa S, Misawa S, Hattori T. Focal shoulder seizures due to an acute small cortical infarction located medial to precentral knob. *J Neurol*. 2006;253:963–964.
26. Schwarz N, Kuniss M, Nedelmann M, Kaps M, Bachmann G, Neumann T, Pitschner HF, Gerriets T. Neuropsychological decline after catheter ablation of atrial fibrillation. *Heart Rhythm*. 2010;7:1761–1767.
27. Estes NA 3rd. Neuropsychological effects of atrial fibrillation catheter ablation: a manifestation of the occult? *Heart Rhythm*. 2010;7:1768–1769.
28. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL, Day JD. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *J Cardiovasc Electrophysiol*. 2011;22:839–845.
29. Kidwell CS, Alger JR, Di Salle F, Starkman S, Villablanca P, Bentson J, Saver JL. Diffusion MRI in patients with transient ischemic attacks. *Stroke*. 1999;30:1174–1180.

CLINICAL PERSPECTIVE

Left atrial catheter ablation of the pulmonary veins is a well-established therapeutic approach to abolish symptomatic atrial fibrillation. Although ablation-related ischemic strokes or transient ischemic attacks are rare, recent case series have demonstrated MRI-detected ischemic brain lesions in 4% to 41% of all patients without obvious neurological deficits immediately after the ablation procedure. These MRI findings have caused safety concerns among treating physicians and patients. However, little is known about the possible cognitive side effects of ablation-related brain ischemia. Follow-up data of the prospective single-center Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal Atrial Fibrillation study show that there was no detectable effect of left atrial catheter ablation on cognitive function in 37 patients undergoing 41 ablation procedures, irrespective of the presence or persistence of ablation-related ischemic brain lesions. Interestingly, the vast majority of the acute ischemic brain lesions after ablation did not lead to persistent glial scars after 6 months.

Neuropsychological Effects of MRI-Detected Brain Lesions After Left Atrial Catheter Ablation for Atrial Fibrillation: Long-Term Results of the MACPAF Study

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SUPPLEMENTAL MATERIAL

Supplemental Table 1 Neuropsychological assessment pre-ablation and 6 months post-ablation according to presence of DWI lesions. p values based on the Mann-Whitney test comparing the computed individual difference of neuropsychological test results pre-ablation and 6 months post-ablation across groups. Values are expressed as median (IQR).

	DWI lesion post-ablation (n=16/18)	No DWI lesion post-ablation (n=23)	p
Attention & executive functions			
Trail-making test A; s	-10 (-16 - +8)	+2 (-7 - +17)	0.141
Trail-making test B; s	-5 (-46 - +12)	-9 (-18 - +17)	0.493
Color-word-interference test; s	-22 (-50 - -3)	-8 (-26 - +7)	0.217
Category Fluency; n	+4 (0 - +6)	+2 (-3 - +4)	0.367
Letter Fluency; n	+1 (-2 - +7)	+1 (-4 - +2)	0.235
Digit-span backward; points	0 (-1 - +1)	+1 (-1 - +2)	0.181
Short Term Memory			
Digit-span forward; points	0 (-1 - +1)	0 (-1 - +1)	0.704
Learning (verbal & non-verbal)			
RAVLT [*] ; n	+1 (-3 - +5)	+1 (-1 - +2)	0.797
ROC Figure [†] ; points	+2 (0 - +4)	+1 (-2 - +3)	0.358
Reasoning			
LPS 50 [‡] ; points	+1 (0 - +3)	+2 (-1 - +4)	0.696

^{*} Rey Auditory Verbal Learning Test (German Version); delayed recall (A7); [†] Rey-Osterrieth Complex Figure; immediate recall; [‡] Subtest 3 from the German Leistungsprüfungssystem (LPS)

Supplemental Table 2 Neuropsychological assessment pre-ablation and 6 months post-ablation in patients with MRI-detected acute brain lesions post-ablation according to persistence of brain lesions. p values based on the Mann-Whitney test comparing the computed individual difference of neuropsychological test results pre-ablation and 6 months post-ablation across groups. Values are expressed as median (IQR).

	DWI lesion (n=33/34)	No lesion (n=6/7)	p
Attention & executive functions			
Trail-making test A; s	+8 (+1 - +14)	-3 (-12 - +8)	0.134
Trail-making test B; s	+7 (-14 - +11)	-12 (-19 - +14)	0.499
Color-word-interference test; s	-17 (-24 - +5)	-9 (-32 - +7)	0.886
Category Fluency; n	+1 (-6 - +4)	+2 (-1 - +6)	0.295
Letter Fluency; n	0 (-4 - +4)	+1 (-3 - +4)	0.761
Digit-span backward; points	-1 (-1 - 0)	0 (-1 - +2)	0.221
Short Term Memory			
Digit-span forward; points	-1 (-1 - +2)	0 (-1 - +1)	0.742
Learning (verbal & non-verbal)			
RAVLT [‡] ; n	+3 (-1 - +5)	0 (-2 - +3)	0.207
ROC Figure [†] ; points	+2 (-2 - +5)	+1 (-2 - +4)	0.630
Reasoning			
LPS 50 [‡] ; points	+1 (-2 - +2)	+2 (0 - +3)	0.334

[‡]Rey Auditory Verbal Learning Test (German Version); delayed recall (A7); [†]Rey-Osterrieth Complex Figure; immediate recall; [‡]Subtest 3 from the German Leistungsprüfungssystem (LPS)