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BRIEF COMMUNICATION

New Cerebral Microbleeds After Catheter-Based Structural Heart Interventions: An Exploratory Analysis

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BACKGROUND: Cerebral microbleeds (CMBs) are increasingly recognized as "covert" brain lesions indicating increased risk of future neurological events. However, data on CMBs in patients undergoing catheter-based structural heart interventions are scarce. Therefore, we assessed occurrence and predictors of new CMBs in patients undergoing catheter-based left atrial appendage closure and percutaneous mitral valve repair using the MitraClip System.

METHODS AND RESULTS: We conducted an exploratory analysis using data derived from 2 prospective, observational studies. Eligible patients underwent cerebral magnetic resonance imaging (3 Tesla) examinations and cognitive tests (using the Montreal Cognitive Assessment) before and after catheter-based left atrial appendage closure and percutaneous mitral valve repair. Forty-seven patients (53% men; median age, 77 years) were included. New CMBs occurred in 17 of 47 patients (36%) following catheter-based structural heart interventions. Occurrences of new CMBs did not differ significantly between patients undergoing catheter-based left atrial appendage closure and percutaneous mitral valve repair (7/25 versus 10/22; P=0.348). In univariable analysis, longer procedure time was significantly associated with new CMBs. Adjustment for heparin attenuated this association (adjusted odds ratio [per 30 minutes]: 1.77 [95% CI, 0.92–3.83]; P=0.090).

CONCLUSIONS: New CMBs occur in approximately one-third of patients after catheter-based left atrial appendage closure and percutaneous mitral valve repair using the MitraClip System. Our data suggest that longer duration of the procedure may be a risk factor for new CMBs. Future studies in larger populations are needed to further investigate their clinical relevance.

CLINICAL TRIAL REGISTRATION: German Clinical Trials Register: DRKS00010300 (https://drks.de/search/en/trial/DRKS00010300); ClinicalTrials.gov : NCT03104556 (https://clinicaltrials.gov/ct2/show/NCT03104556?term=NCT03104556&draw=2&rank=1).

Key Words: catheter-based structural heart interventions ■ cerebral microbleeds ■ left atrial appendage closure ■ mitral valve repair (MVR) using the MitraClip System

Cerebral microbleeds (CMBs), detected on blood-sensitive magnetic resonance imaging (MRI) sequences, are markers of bleeding-prone microangiopathies (particularly hypertensive vasculopathy and cerebral amyloid angiopathy [CAA]). They have been commonly observed in patients with cerebrovascular diseases and are associated with an increased risk for intracerebral hemorrhage and ischemic stroke.[1]

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In patients with acute ischemic stroke, new CMBs occur in ≈4% of patients after receiving intravenous thrombolysis and stroke patients with new CMBs have an increased risk for intravenous thrombolysis–related hemorrhagic complications.[2] Even more frequently than in ischemic stroke patients with intravenous thrombolysis treatment, new CMBs are reported in patients undergoing cardiac surgery with cardiopulmonary bypass.[3,4] So far, data on CMBs in patients undergoing catheter-based structural heart interventions and their clinical relevance[1,5] are scarce.[6] Therefore, the aim of this exploratory analysis was to assess occurrence and predictors of new CMBs in 2 cohorts of patients undergoing different catheter-based, left-sided structural heart interventions.

METHODS

Data Availability Statement

Anonymized data can be shared upon reasonable request (of note: imaging data are not publicly available as they contain information that could compromise patient privacy). Data sharing will be restricted to noncommercial and academic purposes only.

Data Sources and Study Populations

This analysis includes data derived from 2 prospective, observational, single-center studies, including patients undergoing catheter-based left atrial appendage closure (LAAC data set)[7] and percutaneous mitral valve repair (MVR) using the MitraClip System (MitraClip data set).[8]

Patients undergoing catheter-based LAAC had paroxysmal, persistent, or permanent atrial fibrillation and at least 1 relative or absolute contraindication to long-term oral anticoagulation.[7] Patients undergoing percutaneous MVR using the MitraClip System had heart failure and moderate/severe mitral regurgitation.[8] To unequivocally detect new CMBs after these procedures, eligible patients for this exploratory analysis had to receive 2 cerebral MRI examinations—before and after the catheter-based structural heart intervention—on the same MRI scanner (Figure 1).

Recruitment was performed at the Charité—Universitätsmedizin Berlin, Campus Benjamin Franklin, between May 2016 and May 2017 (LAAC data set; German Clinical Trials Register: DRKS00010300)[7] and between June 2017 and September 2019 (MitraClip data set; ClinicalTrials.gov: NCT03104556).[8] Both prospective, observational studies were approved by the local Ethics Committee of the Charité—Universitätsmedizin Berlin, Germany (LAAC data set: EA/084/15; MitraClip data set: EA2/005/17). All patients gave written informed consent.[7,8]

LAAC Procedure, MitraClip Procedure

Catheter-based LAAC and percutaneous MVR using the MitraClip System were performed in standard fashion as described previously.[7,8] During both procedures, repeated boluses of unfractionated heparin were administered aiming at an activated clotting time

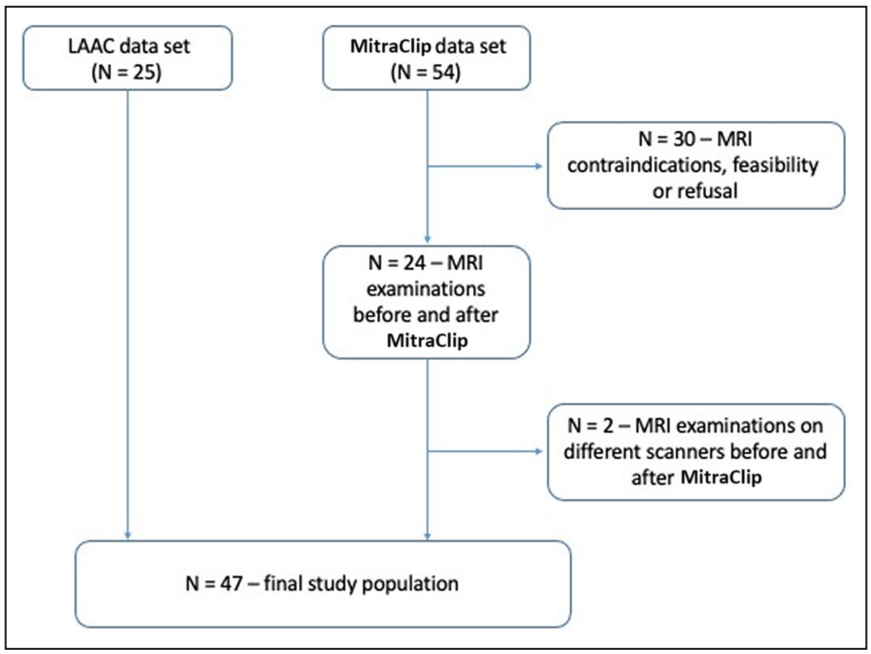

Figure 1. Flowchart of the study population.
LAAC indicates left atrial appendage closure; and MRI, magnetic resonance imaging.

>250 seconds. LAAC (using the Amulet [Abbott, Menlo Park, CA], Occlutech [Occlutech, Jena, Germany], or Lambre [Lifetech Scientific, Shenzhen, China] devices) was performed under conscious sedation, MVR using the MitraClip System (Abbott) was performed under conscious sedation (n=4) or general anesthesia (n=18).

Clinical Data

Baseline characteristics were extracted from the medical records (including sex, age, vascular risk factors, laboratory data, and medication on admission). As previously reported,[8] the severity of mitral regurgitation was graded as mild (I), moderate (II), or severe (III). Cognitive tests were performed before and after the catheter-based structural heart interventions using the Montreal Cognitive Assessment.[9] Follow-up testing was performed when general anesthesia or conscious sedation was completely reversed.

Cerebral MRI (Imaging Protocol and Image Analysis)

Cerebral MRI examinations were performed before and after the catheter-based structural heart interventions using 3 Tesla MRI scanners (Tim Trio, Siemens Medical, Erlangen, Germany; Skyra, Siemens Medical; Prisma Fit, Siemens Medical). We acquired T2*-weighted imaging (slice thickness, 5 mm), diffusion-weighted imaging, and axial fluid-attenuated inversion recovery imaging.[2,7,8]

CMB analysis was performed as previously described[2]: according to consensus recommendations, CMBs were defined as small (up to 10 mm in diameter), round or oval hypointense lesions with associated blooming being at least half-surrounded by brain parenchyma.[10] The T2*-weighted MRIs (before and after the catheter-based structural heart intervention) were coregistered using SPM12 (reference: T2*-weighted MRI before procedure). With focus on CMBs, all MRIs were rated by 1 experienced rater (T.B.B.; >1 year of supervised training in diagnostic neuroradiology) blinded to clinical information. The results were subsequently compared with the MRI evaluation from routine clinical practice (performed by K.V., I.G., or J.B.F.; each >10 years of work experience in diagnostic neuroradiology). In cases of disagreement, a third rater (K.V. or J.B.F.) was consulted. The CMB occurrence, number, and anatomical distribution were analyzed using the T2*-weighted sequences acquired before the procedure. Newly occurring CMBs were assessed using a slice-by-slice comparison of the corresponding T2*-weighted MRIs before and after the procedure (Figure 2). The CMB distribution (lobar, deep, infratentorial, or mixed) was categorized according to established patterns.[11] In patients with new ischemic brain lesions after the procedure (as seen on diffusion-weighted imaging), newly appearing CMBs in the acute infarcted area were not classified as new CMBs.[2]

Intracerebral (macro)hemorrhage (ICH) was assessed on T2*-weighted imaging. Chronic ischemic lesions, high-degree (>20) centrum semiovale/basal ganglia enlarged perivascular spaces,[10,12] lacunes of presumed vascular origin[10] and severity of white matter hyperintensities of presumed vascular origin (using the Wahlund visual scale) were assessed on fluid-attenuated inversion recovery images.[8]

Statistical Analysis

For continuous variables, we used the Wilcoxon test. For categorical variables, we used the chi-squared test (with Yates' continuity correction). In addition, we performed a multivariable logistic regression analysis using the Firth logistic regression method to calculate odds ratios and corresponding 95% CIs for the risk of new CMBs after the catheter-based structural heart interventions. The Firth logistic regression method was used because of the small sample size (n=47). Variables were included in the multivariable logistic regression model if univariable analysis suggested an association with $P<0.1$. For all analyses, we used a 2-sided significance level of 0.05. All analyses were performed using the R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

The corresponding author had full access to all the data in the study and takes responsibility for their integrity and the data analysis.

RESULTS

Patient Characteristics

Between 2016 and 2017, 25 consecutive patients who had received LAAC underwent 2 cerebral MRI examinations (ie, before and after LAAC). Accordingly, between 2017 and 2019, 24 consecutive patients who had received MitraClip underwent 2 cerebral MRI examinations. Of these, 2 patients were examined on different MRI scanners before and after the MitraClip procedure (Figure 1). Thus, 47 patients (53% men; median age, 77 [interquartile range (IQR), 70–83] years) were included in the final analysis.

Compared with patients undergoing the MitraClip procedure, patients undergoing LAAC more often had atrial fibrillation (100% versus 46%; $P<0.001$), a history of ICH (36% versus 5%; $P=0.023$), and arterial hypertension (100% versus 77%; $P=0.041$). MitraClip and patients undergoing LAAC did not differ significantly regarding age, sex, and other vascular risk factors (diabetes, coronary artery disease, history of percutaneous coronary intervention, coronary artery bypass surgery, or ischemic stroke/transient ischemic attack).

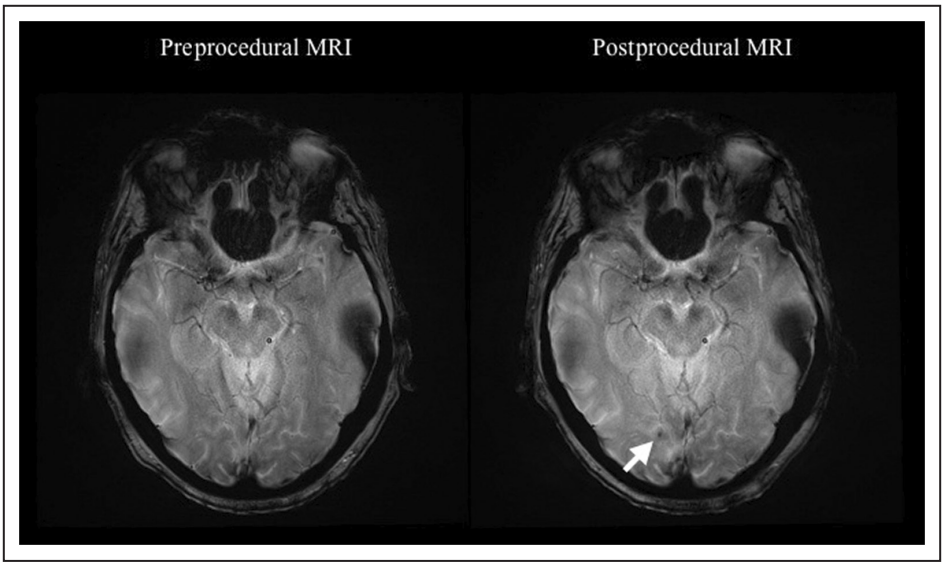

Figure 2. New cerebral microbleed after catheter-based structural heart intervention.
MRI indicates magnetic resonance imaging.

Frequency of CMBs Before and After the Catheter-Based Structural Heart Interventions

Cerebral MRI examinations were performed 1 day before (median [IQR, 0–1]) and 1 day after (median [IQR, 1–3]) the catheter-based, left-sided structural heart interventions.

CMBs on preprocedural MRI were present in 28 of 47 patients (60%). Of these, 13 patients had 1 CMB, 8 patients had 2 to 4 CMBs, and 7 patients had ≥5 CMBs before the procedure. Distribution of CMBs was strictly lobar in 12 patients, strictly deep in 6 patients, strictly infratentorial in 1 patient, and mixed in 9 patients. Although not statistically significant, patients with preexisting CMBs had numerically more often atrial fibrillation (58% versus 86%; *P*=0.071) and a history of ICH (5% versus 32%; *P*=0.065).

New CMBs after the catheter-based structural heart interventions occurred in 17 of 47 patients (36%). Of these, 15 patients had 1 new CMB, and 2 patients had 2 new CMBs. Distribution of new CMBs was strictly lobar in 14 patients, strictly deep in 1 patient, and strictly infratentorial in 2 patients. The frequency of new CMBs did not differ significantly between patients undergoing catheter-based LAAC (7/25) and percutaneous MVR using the MitraClip System (10/22; *P*=0.348; Table).

Factors Associated With Occurrence of New CMBs

In univariable analysis, patients with and without new CMBs after the catheter-based structural heart interventions differed regarding procedure time (the procedure time was longer in patients with new CMBs). In addition, there was a signal toward higher cumulative heparin dosages in patients with new CMBs (compared with patients without new CMBs), but this did not reach the predefined statistical significance level (10 000 IU of heparin [median IQR, 8000–14 000] versus 7500 IU heparin [median; IQR, 7000–10 000]; *P*=0.065). Patients with and without new CMBs did not differ significantly regarding preexisting CMBs (and their distribution), as well as medication on admission, anesthetic regime, blood pressure, or activated clotting time during the procedures (Table).

In an exploratory multivariable logistic regression analysis, the association between new CMB and procedure time was attenuated and just failed to reach statistical significance (adjusted odds ratio [per 30 minutes], 1.77 [95% CI, 0.92–3.83]; *P*=0.090; adjusted for heparin).

Outcome Parameters

No new ICH was detected on postprocedural MRI.

New ischemic lesions after the catheter-based structural heart interventions were present in 32 of 47 (68%) of patients on postprocedural MRI. Occurrence of new ischemic lesions did not differ in patients with and without new CMBs (12/17 versus 20/30; *P*=1.000; Table).

Cognitive tests were performed 1 day before (median [IQR, 0–1]) and 1 day after (median [IQR, 1–3]) the catheter-based structural heart interventions. The median preprocedural Montreal Cognitive Assessment score was 25 (IQR, 21–27), the median postprocedural Montreal Cognitive Assessment score was 24 (IQR, 20–26).

Table. Comparison of Patients Without and With New Cerebral Microbleeds

	All patients, n=47	No new CMBs, n=30	New CMBs, n=17	*P value*
Demographics				
Age, y, median (IQR)	77 (70–83)	78 (70–85)	77 (71–80)	0.457
Male, n (%)	25 (53)	18 (60)	7 (41)	0.348
Risk factors, n (%)				
Atrial fibrillation	35 (75)	23 (77)	12 (71)	0.912
Diabetes, type 2	16 (34)	12 (40)	4 (24)	0.410
Arterial hypertension	42 (89)	28 (93)	14 (82)	0.496
CAD	28 (60)	18 (60)	10 (59)	1.000
Percutaneous coronary intervention	24 (51)	18 (60)	6 (35)	0.185
Coronary artery bypass surgery	7 (15)	5 (17)	2 (12)	0.978
History of ischemic stroke/TIA	8 (17)	3 (10)	5 (29)	0.194
History of ICH	10 (21)	6 (20)	4 (24)	1.000
On admission				
Platelet aggregation inhibitors, n (%)	21 (45)	12 (40)	9 (53)	0.581
Dual antiplatelet therapy, n (%)	12 (26)	8 (27)	4 (24)	1.000
Oral anticoagulation, n (%)	22 (47)	14 (47)	8 (47)	1.000
Statins*, n (%)	28 (61)	19 (63)	56% (9)	0.879
Creatinine, mg/dL, median (IQR)	1.16 (1.02–1.69)	1.23 (1.01–2.36)	1.11 (1.04–1.31)	0.199
INR, median (IQR)	1.13 (1.07–1.42)	1.15 (1.05–1.70)	1.12 (1.10–1.39)	0.877
MoCA score preprocedural†, median (IQR)	25 (21–27)	25 (21–27)	27 (24–27)	0.502
Related to heart failure				
Severity of preprocedural mitral regurgitation, n (%)				0.258
I	17 (36)	13 (43)	4 (24)	
II	12 (26)	8 (27)	4 (24)	
III	18 (38)	9 (30)	9 (53)	
Preprocedural left ventricular ejection fraction,‡ %, median (IQR)	55 (45–60)	55 (45–60)	55 (44–61)	0.816
Preprocedural MRI findings				
CMB presence on preprocedural MRI, n (%)	28 (60)	17 (57)	11 (65)	0.818
Number of CMBs, n (%)				0.405
0	19 (40)	13 (43)	6 (35)	
1	13 (28)	9 (30)	4 (24)	
2–4	8 (17)	3 (10)	5 (29)	
≥5	7 (15)	5 (17)	2 (12)	
CMBs with a strictly lobar distribution, n (%)	12 (26)	6 (20)	6 (35)	0.420
CMBs with a mixed or strictly deep distribution, n (%)	15 (32)	10 (33)	5 (29)	1.000
Preexisting ischemic brain lesion, n (%)	24 (51)	15 (50)	9 (53)	1.000
Preexisting lacunes of presumed vascular origin,§ n (%)	11 (24)	7 (23)	4 (25)	1.000
High-degree (>20) CSO-EPVS,‖ n (%)	1 (2)	0 (0%)	1 (6)	0.747
High-degree (>20) BG-EPVS,¶ n (%)	4 (9)	3 (10)	1 (6)	1.000
Chronic ICH, n (%)	8 (17)	5 (17)	3 (18)	1.000
Wahlund score,# median (IQR)	8 (5–12)	9 (5–12)	6 (5–12)	0.561

(*Continued*)

Table. Continued

	All patients, n=47	No new CMBs, n=30	New CMBs, n=17	*P value*
Catheter-based structural heart intervention				
Type of structural intervention				0.348
MitraClip, n (%)	22 (47)	12 (40)	10 (59)	
LAAC, n (%)	25 (53)	18 (60)	7 (41)	
Conscious sedation, n (%)	29 (62)	20 (67)	9 (53)	0.537
Procedure time, 30 min, median (IQR)	2.3 (1.9–3.1)	2.0 (1.8–2.4)	3.0 (2.0–4.0)	**0.022**
Heparin, IU, median (IQR)	8000 (7000–11 000)	7500 (7000–10 000)	10 000 (8000–14 000)	0.065
Median ACT,** s, median (IQR)	268 (247–315)	276 (240–326)	262 (248–291)	0.393
Maximum ACT,†† s, median (IQR)	320 (279–356)	318 (278–372)	320 (293–350)	0.890
Maximum systolic blood pressure,‡‡ mm Hg, median (IQR)	139 (128–151)	138 (128–155)	138 (128–144)	0.836
Maximum diastolic blood pressure,§§ mm Hg, median (IQR)	80 (71–80)	80 (71–80)	80 (75–81)	0.820
Outcomes				
Severity of postprocedural mitral regurgitation,‖‖ n (%)				0.102
0	5 (23)	1 (8)	4 (40)	
I	14 (64)	10 (83)	4 (40)	
II	3 (14)	1 (8)	2 (20)	
MoCA score postprocedural,¶¶ median (IQR)	24 (20–26)	24 (20–26)	26 (23–27)	0.303
New DWI lesion after the procedure, n (%)	32 (68)	20 (67)	12 (71)	1.000

P values were calculated using the Wilcoxon test for continuous variables and the chi-squared test for categorical variables. Bold indicates a statistically significant result. ACT indicates activated clotting time; BG-EPVS, basal ganglia enlarged perivascular spaces; CAD, coronary artery disease; CMBs, cerebral microbleeds; CSO-EPVS, centrum semiovale enlarged perivascular spaces; DWI, diffusion-weighted imaging; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; LAAC, left atrial appendage closure; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; and TIA, transient ischemic attack.

*The variable statins were known in 30 and 16 patients, respectively.
†The variable preprocedural MoCA score was known in 28 and 14 patients, respectively.
‡The variable preprocedural left ventricular ejection fraction was known 30 and 16 patients, respectively.
§The variable preexisting lacunes of presumed vascular origin was known in 30 and 16 patients, respectively.
‖The variable high-degree (>20) CSO-EPVS was known in 30 and 16 patients, respectively.
¶The variable high-degree (>20) BG-EPVS was known in 30 and 16 patients, respectively.
#The variable Wahlund score was known in 30 and 16 patients, respectively.
**The variable median ACT was known in 27 and 16 patients, respectively.
††The variable maximum ACT was known in 27 and 16 patients, respectively.
‡‡The variable maximum systolic blood pressure was known in 28 and 12 patients, respectively.
§§The variable maximum diastolic blood pressure was known in 28 and 12 patients, respectively.
‖‖The variable severity of postprocedural mitral regurgitation was known in 12 and 10 patients, respectively.
##The variable postprocedural MoCA score was known in 28 and 13 patients, respectively.

DISCUSSION

CMBs are a common incidental finding in patients with cerebrovascular diseases and are increasingly recognized as "covert" brain lesions.[1] They may also serve as a surrogate to estimate safety of a given procedure (or a specific periprocedural anticoagulation strategy, such as heparin or bivalirudin). However, data on CMBs in patients undergoing catheter-based structural heart interventions are scarce. For the first time, our study demonstrates that new CMBs occur in a considerable proportion (36%) of patients after catheter-based LAAC and percutaneous MVR using the MitraClip System. In comparison with the available literature, our data suggest that new CMBs after catheter-based, left-sided structural heart interventions occur more frequently than after receiving intravenous thrombolysis in patients with acute ischemic stroke (≈4%)[2] but less frequently than after adult cardiac surgery (63%–76%).[3,4]

Interestingly, in a recently published prospective study, new CMBs occurred in 23% of 84 patients after transcatheter aortic valve replacement (TAVR).[6] Longer procedure time was associated with occurrence of new CMBs in the above-mentioned transcatheter aortic valve replacement study[6] as well as in our univariable analysis (although this association was attenuated in our multivariable analysis), suggesting that procedure-related effects may be involved in the

development of new CMBs. The positive association between occurrence of new CMBs and longer procedure time is further supported by another recently published study that linked occurrence of postoperative CMBs to key procedural aspects of thoracic endovascular aortic repair.[13]

In certain contexts, strictly lobar CMBs are strongly associated with CAA[1,14]—whether newly occurring, postinterventional CMBs are also attributable to CAA is currently uncertain.[15] Interestingly, Patel et al[3] reported that new CMBs after adult cardiac surgery occurred in all examined patients with the diagnosis of probable CAA according to the modified Boston criteria[14] on presurgery MRI. Breiding et al[15] reported that distribution of susceptibility weighted imaging lesions on postinterventional MRI was suggestive of possible or probable CAA according to the modified Boston criteria[14] in a relevant percentage of patients with artificial heart valves. In the present study, new CMBs predominantly had a lobar distribution, although preexisting CMBs with a strictly lobar distribution were not significantly associated with occurrence of new CMBs. In conclusion, the current data are not yet sufficient to determine the underlying mechanism of newly occurring, postinterventional CMBs. Histopathology studies may be helpful to further elucidate the pathophysiological entity of these newly occurring lesions. In accordance with the Standards for Reporting Vascular Changes on Neuroimaging criteria[10] and in consensus among the raters, we have deliberately chosen to classify these lesions as CMBs, although differential considerations (eg, small embolized calcifications or—depending on the material used—consequences of microabrasion from endovascular material[15]) should be noted.

Although CMBs have been identified as a risk factor for ischemic stroke and ICH in patients with cerebrovascular diseases,[1,2] this could not be shown in the present study (no significant association between new CMBs and concomitant new ischemic lesions, no new ICH on follow-up MRI). Regarding the influence of newly occurring CMBs on cognition, we decided not to perform an inferential statistical analysis because of the limited number of patients, the high rate of concomitant new ischemic lesions (68%) and the early assessment of the cognitive tests after the catheter-based structural heart intervention. A long-term follow-up (to exclude a possible influence of the anesthetic regime) as well as a larger sample size and a more comprehensive neurocognitive assessment are necessary to investigate the effect of newly occurring CMBs after catheter-based structural heart interventions on cognition in detail. Nevertheless, it can be stated that despite the high proportion of patients with new diffusion-weighted imaging lesions in our study, no large negative shift in the cognitive function occurred. Moreover, taking into account possible postsedation effects, these would be expected to rather worsen the results and amplify rather than attenuate the shift.

Another interesting aspect is the high frequency (60%) of preexisting CMBs in our study cohort. Until recently,[6] data on (preexisting) CMBs were mainly derived from population-based cohorts as well as from patients with ischemic stroke, ICH, or dementia.[1] Our data call for further studies to determine the prevalence and clinical relevance of CMBs in different cardiovascular risk populations.

Limitations of this analysis have to be noted. First, this is an exploratory analysis including data from 2 single-center, catheter-based structural heart intervention studies that differed in several baseline characteristics (prior ICH, atrial fibrillation, arterial hypertension). Reassuringly, our results are consistent with a recently published study investigating the occurrence of new CMBs after transcatheter aortic valve replacement.[6] Nevertheless, the results of our analysis can only be considered hypothesis generating. Second, because of the small sample size, type II error must be taken into account. Third, we used T2*-weighted imaging (slice thickness of 5 mm) at 3.0 Tesla to detect CMBs. Therefore, small CMBs might have been missed. Fourth, because of the exploratory nature of the analysis, few data are missing (eg, activated clotting time was known in 43/47 patients, severity of postprocedural mitral regurgitation was known in 22/47 patients). Fifth, only data from patients without MRI contraindications could be used for the present analysis, leaving a potential risk of selection bias.

In conclusion, newly occurring hypointense lesions on T2*-weighted MRI fulfilling the criteria of CMBs occur in approximately one-third of patients after catheter-based LAAC or percutaneous MVR using the MitraClip System. In univariable analysis, longer procedure time was the prominent risk factor for occurrence of new CMBs. Occurrence of new CMBs was not associated with concomitant new ischemic lesions on MRI. Future studies with larger cohorts and long-term follow-up should further elucidate the clinical relevance of new CMBs in patients undergoing catheter-based, left-sided structural heart interventions.

ARTICLE INFORMATION

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