Asymptomatic cerebral lesions during pulmonary vein isolation under uninterrupted oral anticoagulation

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Aims

Left atrial radiofrequency ablation has been shown to carry a risk of asymptomatic cerebral lesions. No data exist in patients under continued oral anticoagulation during the ablation procedure. The aim of this study was to quantify the amount of silent cerebral lesions assessed by pre-procedural and post-procedural magnetic resonance imaging (MRI) in patients under therapeutic international normalized ratio (INR) and to identify clinical or procedural parameters that correlate with cerebral embolism.

Methods and results

A total of 131 consecutive patients undergoing catheter ablation for paroxysmal (n = 80, 61.1%) or persistent (n = 51, 38.9%) atrial fibrillation were included in the study. Pulmonary vein antrum isolation (PVI), roofline, mitral isthmus line, and complex fractionated atrial electrogram (CFAE) ablation using 3.5 mm open-irrigated tip catheters were performed, as needed. All patients underwent pre-procedural and post-procedural cerebral MRI. Post-procedural MRI revealed new embolic lesions in 16 patients (12.2%), all of them asymptomatic. Clinical parameters showing a significant correlation with cerebral embolism in univariate analysis were age (P = 0.027), persistent atrial fibrillation (vs. paroxysmal; P = 0.039), and spontaneous echo contrast in transesophageal echocardiography (P = 0.029). Significant procedural parameters were electric cardioversion (P = 0.041), PVI only (P = 0.008), and ablation of complex atrial electrograms (P = 0.005). Independent risk factors in multivariate analysis were age (P = 0.009), spontaneous echo contrast (P = 0.029) and CFAE ablation (P = 0.006).

Conclusion

Radiofrequency ablation in patients under continued oral therapeutic anticoagulation is associated with a substantial risk of silent embolism detected by cerebral MRI. Therefore, continuation of oral anticoagulation is not able to prevent cerebral embolism. A variety of different clinical and procedural factors seem to contribute to the risk of cerebral lesions.

Keywords

Atrial fibrillation • Radiofrequency catheter ablation • Cerebral embolism • Oral anticoagulation • Magnetic resonance imaging

Introduction

Radiofrequency catheter ablation (RFCA) with isolation of the pulmonary veins (PVs) is an accepted method for treatment of highly symptomatic and drug-refractory atrial fibrillation (AF). Large cohort studies showed that the risk of stroke is increased approximately five-fold in AF patients compared with sinus rhythm. The incidence of symptomatic cerebral thromboembolic complications [stroke and transient ischaemic attack (TIA)] in pulmonary vein isolation (PVI) has been shown to be in the range of 0.5–0.94% according to the worldwide surveys and retrospective data. Recent data have shown that PVI additionally carries a
substantial risk of silent or asymptomatic cerebral lesions ranging between 4.3 and 38.9% depending on the energy source used.\textsuperscript{5–9} Within these reports, the use of RFCA with open irrigation as the most widely used energy source in PVI showed silent cerebral lesions in 6.8–14%.\textsuperscript{5–9}

All previous studies stopped oral anticoagulation prior to the RFCA procedure using low-molecular-weight heparin (LMWH) bridging and continuous intravenous (i.v.) heparin in the peri procedural phase. Our aim was to assess the effect of continued oral anticoagulation throughout the procedure on asymptomatic cerebral lesions. The hypothesis of this study was to avoid clotting on the sheaths and catheters around the transseptal puncture till a therapeutic activated clotting time (ACT) is reached. In addition, no pause in anticoagulation within the first hours after removal of the sheaths would occur. In contrast, other possible sources of embolism such as air embolism or thermal clotting should not be altered by continued oral anticoagulation.

In this single-centre study, we prospectively performed pre- and post-procedural cerebral MRI in patients undergoing RFCA for paroxysmal or permanent AF on continued therapeutic oral anticoagulation.

Methods

Study population

The study population consisted of 140 consecutive patients presenting to the Elisabethinen University Teaching Hospital Linz for PVI from June 2011 to February 2012. Radiofrequency catheter ablation was performed in patients with symptomatic paroxysmal or persistent AF refractory to at least one antiarrhythmic drug. Nine patients were excluded from the study due to claustrophobia or non-MRI-safe pacemakers rendering the MRI studies impossible. All patients gave informed consent to the additional pre- and post-procedural MRI investigations and to the study protocol.

Study design

Patients were admitted to the hospital 2 days before ablation. All patients underwent a thorough physical examination including their neurological status. Administration of oral anticoagulation (Phenprocoumon) was started at least 6 weeks prior to ablation to maintain a stable international normalized ratio (INR) between 2.0 and 3.0. Oral anticoagulation was continued throughout the procedure with a targeted low-therapeutic INR (2.0–2.5) at the day of procedure. If INR was more than 3.0, vitamin K was administered or the vitamin K antagonist was simply paused and INR was re-checked. As patients were hospitalized 2 days prior to the procedure, there generally was sufficient time to reach the INR goals. Only if INR was <2.0 at the day of or the day after procedure, subcutaneous LMWH was given at weight-adjusted doses until INR was therapeutic again for at least 2 days.

All patients underwent pre-procedural MRI within 48 h prior to RFCA as well as post-procedural MRI within 24 h after ablation. If a cerebral lesion was detected, patients underwent a thorough neurological examination by an experienced neurologist and another MRI study was scheduled 3 months later for long-term follow-up.

Pulmonary vein isolation: ablation approach

All RCFA were performed using a three-dimensional electroanatomic mapping system with computed tomography integration (CartoMerge, Biosense Webster, Diamond Bar, CA, USA or NavX, St Jude Medical, St Paul, MN, USA) as previously described.\textsuperscript{10–14} Using a transfemoral venous approach an octopolar catheter was placed in the coronary sinus (EP XT, BARD Electrophysiology, Lowell, MA, USA). After a single transseptal puncture, a retrograde angiography of the PVs was performed. For mapping and ablation a 3.5 mm open-irrigated tip quadripolar catheter (Navistar Thermocool or Thermocool SmartTouch\textsuperscript{TM}, Biosense Webster, Therapy CoolPath or Therapy Coolflex\textsuperscript{TM}, St Jude Medical) was used. To prove electrical disconnection between the left atrium (LA) and the PV, a ring-shaped multipolar diagnostic catheter (Lasso, Biosense Webster, or Optima) was introduced into the different PV to show entry and exit block. Both catheters were inserted through the single transseptal puncture using the sheath for the ring-shaped catheter and introducing the ablation catheter ‘shearthless’ in parallel to the sheath through the puncture hole. Thereby, multiple catheter exchanges were avoided, despite the use of a single transseptal puncture technique. The ring-shaped catheter remained in the LA during the whole procedure; the transseptal sheath could be pulled back to the right side at operator’s decision.

We performed circumferential PV ablation\textsuperscript{12} with the addition of further linear lesions\textsuperscript{10,13} (roof line, mitral isthmus line, and inferior line starting from the coronary sinus) and focal radiofrequency applications at areas with complex fractionated atrial electrograms (CFAEs), as depicted by an automated dedicated software of the Carto or NavX System.\textsuperscript{14} Lines and CFAE ablation were only used in case AF could not be terminated by PV ablation. If AF still was persistent after linear or CFAE ablation patients were electrically cardioverted at the end of procedure to be able to verify entry and exit block from the PV and to check for completeness of linear lesions. Electrical disconnection of the PV including both entrance and exit block had to be documented as this has been shown to be crucial for long-term success.\textsuperscript{15}

The following hardware settings were used for our procedure: maximum temperature 43°C, maximum energy 25 W at the posterior LA wall and 30–35 W in other locations. The irrigation flow rate was 20–30 mL/min. We used a continuous catheter dragging method with single lesion duration of 20–30 s.

Deep sedation using i.v. fentanyl, midazolam, and propofol was used as standard approach; general anaesthesia was performed in only three patients presenting with a sleep apnoea condition.

Anticoagulation during ablation

After performing the initial groin venous punctures, all patients received unfractionated i.v. heparin as a bolus of 3 000 IU before transseptal puncture. Directly after the transseptal puncture, another bolus of i.v. heparin was given to add up to 100 IU/kg body weight (i.e. additional 7 000 IU for a 100 kg patient to add up to 100 × 100 IU = 10 000 IU). During the RFCA procedure, the targeted ACT between 300 and 400 s was maintained by a continuous i.v. heparin infusion or additional boluses as needed. Activated clotting time was checked every 20–30 min. The transseptal sheath was continuously flushed with heparinized saline (2 IU/mL; flow-rate: 3 mL/min).

After the procedure, all sheaths were removed without a waiting period or antagonization with protamine. Pericardial effusion was excluded directly after the procedure by echocardiography.

Cerebral magnetic resonance imaging

Cerebral MRI was performed using a 1.5 T scanner (Siemens, Erlangen, Germany). The detailed cerebral MRI protocol has been reported by another study group.\textsuperscript{2,6} Briefly, the imaging protocol consisted of
(i) a transversal diffusion weighted sequence and (ii) a transversal T2* weighted sequence. In post-ablation MRI, acute embolic lesions were defined as new focal hyperintense areas detected by the diffusion weighted sequence due to a restricted diffusion signal. The size, number, and location of each cerebral lesion were reported.

Statistical analysis
Continuous variables are presented as mean ± standard deviation, categorical data as counts or percentages. Comparing groups, we used cross tabulations for nominal variables performing χ², Cramer’s V, or Fisher’s exact test for small sample sizes, when applicable. Student’s t-test for independent samples with a confidence interval of 95% was used for metric variables.

A stepwise multivariate logistic regression model including all parameters showing significant P values in univariate analysis was used to test the independent correlation of these parameters with new cerebral lesions.

Values of P < 0.05 were considered significant; values between 0.05 and 0.1 were reported as a trend to significance.

IBM SPSS statistics 20 package was used for calculations (IBM, SPSS Inc., Chicago, IL, USA).

Results
A total of 131 patients were included in the study. Ninety-two patients (70%) were male with a mean age of 59.5 ± 8 years, predominantly paroxysmal AF (61.1%), a mean of 1.4 ± 0.8 (range 1–4) failed antiarrhythmic drugs, and a prior history of AF of 50 ± 63 (range 2–420) months. The thromboembolic risk as assessed by the CHADS2 or CHA2DS2-VASc-Scores was rather low showing a mean of 0.9 ± 0.9 or 1.5 ± 1.3, respectively. The most prevalent cardiac risk factors in this population were arterial hypertension (56.5%), dyslipidaemia (52.7%), and coronary disease (20.6%); mean body mass index (BMI) was 28.4 ± 4.9.

Thirteen patients (9.9%) had a history of prior cerebrovascular events, such as TIA or stroke. Pre-procedural MRI was able to detect cerebral lesions in only eight (61.5%) of these patients. A high prevalence (40.5%) of pre-procedural pathology (white matter lesions, intracerebral calcifications, and scar) with 13% of true intracerebral scar was evident in our patient population.

Sixteen patients (12.2%) revealed new silent embolic lesions in post-procedural MRI (Figure 1), no periprocedural symptomatic cerebrovascular event was detected. The mean number of lesions in each patient was 1.6 ± 1.3 (range 1–6). In total, 25 new cerebral embolisms were detected, showing 14 small (<3 mm), 10 medium lesions (4–10 mm), and a single large lesion (>10 mm). Sixteen lesions were located cortical or subcortical and distributed over both hemispheres (left side: one frontal, three parietal, three temporal, one occipital; right side: two frontal, three parietal, two temporal, one occipital; one left-sided periventricular), whereas nine lesions were located in the cerebellum (three left-sided, five right-sided). Only one patient revealed six cerebral lesions; all other positive patients only showed one or two lesions.

The patient suffering six new lesions was a 50-year-old man with a CHA2DS2-VASc-Score of only 1 (arterial hypertension) and persistent AF since 1 year. Pre-procedural transesophageal echocardiography (TEE) did reveal low flow velocities and spontaneous echo contrast in the LA. Pulmonary vein isolation, roofline, mitral isthmus line, and CFAE ablation were performed and did not result in conversion to sinus rhythm. Therefore, the patient was cardioverted at the end of procedure. International normalized ratio at the day of procedure was 2.24; ACT times during procedure were unremarkable (362, 343, 352, and 347 s). Procedure time (215 min) and LA time (200 min) were rather long, as expected in this extensive ablation procedure.

All patients showing new cerebral lesions in post-procedural MRI revealed normal neurological examinations by an experienced neurologist. A decline in cognitive function could not be examined owing to the lack of pre-procedural data.

Clinical parameters showing a significant correlation to thromboembolic lesions in univariate analysis were age of the patient, type of AF, and spontaneous echo contrast in TEE prior to ablation (Table 1). In addition, BMI, scar in pre-procedural MRI, and CHA2DS2-VASc-Score showed a trend to significance.
Procedural parameters with a significant impact on silent embolism in univariate analysis were PVI only (reduced risk), CFAE ablation, and longer procedure times (Table 2). The rate of embolism corresponding to the ablation technique performed was 4/74 for PVI only, 8/50 for additional linear lesions, and 6/19 for CFAE ablation (Figure 2). The use of advanced catheter-tip irrigation technology was not able to reduce silent embolism (11.6% of lesions—7 out of 60 patients—with the use of CoolFlex.
Cerebral lesions in PVI under uninterrupted oral Anticoagulation

Figure 2 Rate of silent embolism corresponding to the ablation technique.

Table 3 Multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI, lower limit of OR</th>
<th>95% CI, upper limit of OR</th>
<th>P</th>
</tr>
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<tr>
<td>Mean Age (year)</td>
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<td>1.03</td>
<td>1.24</td>
<td>0.009</td>
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<td>Spontaneous echo contrast in TEE</td>
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<td>1.20</td>
<td>25.44</td>
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<td>CFAE</td>
<td>6.66</td>
<td>1.73</td>
<td>25.64</td>
<td>0.006</td>
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Overall multivariate model fit: P = 0.0004; variables not included in the model: type of AF, procedure time, and PVI only.
CFAE, complex fractionated atrial electrograms; PVI, pulmonary vein isolation; TEE, transesophageal echocardiography.

Discussion

The key finding of our study is the fact that continued oral anticoagulation is not able to abolish the risk of silent cerebral embolism during RFCA using open-irrigated tip catheters. Consequently, the 12.2% risk in our series of 131 patients lies well within previously reported data in studies using LMW heparin bridging (6.8–14%).5–7,9 This gives a hint that conventional thrombus formation is not the only cause of silent embolism.

Independent risk factors in multivariate analysis were age, spontaneous echo contrast, and CFAE ablation. Univariate analysis also showed that longer procedure times, extensive lesion sets (more than PVI), and persistent AF patients had a higher risk. In our opinion, these findings should lead to a more cautious selection and careful consent of elderly patients for AF ablation, to an even stricter anticoagulation regimen in patients showing spontaneous echo contrast in TEE, and to a more restrictive use of extensive lesion sets such as CFAE ablation and in persistent AF cases, posing patients to longer procedure times.

Despite the low incidence of symptomatic stroke in RFCA (0.3–0.7%), the evidence of silent embolism is worrisome in a population already at high risk for cerebral embolism and dementia.2,3 Considering that post-procedural MRI lesions are in any case a sign of brain damage—even if asymptomatic or not detected in follow-up MRI—and that a significant amount of patients will need an additional RFCA procedure, the possible impact of silent stroke cannot be ignored. More data are needed about long-term neurophysiological outcomes and possible preventive actions during catheter ablation of AF.

Pathogenesis of silent embolic lesions

Mechanisms of cerebral embolism include (i) ‘conventional’ clotting at any surface of sheaths or catheters brought into any blood vessel or heart chamber. In addition, (ii) thermal thrombus formation (charring) is possible as charring at the catheter tip or at the surface of the heated tissue. As a third source of micro-emboli (iii) air embolism through sheaths or catheters is possible, especially when exchanging catheters. Another form of air or gas micro-embolism may be caused by (iii) microbubble formation during energy delivery.16

(i) As our findings for RFCA are similar to other reports using LMWH bridging, we do not assume conventional clotting on the sheaths or catheters as the predominant source of microembolism. This type of thrombus should be more effectively prevented by continued oral anticoagulation and heparin bolus administration before transseptal puncture which was not the case in our study.

Residual thrombus in the LA, not seen in TEE, may be another cause of embolism and would be assumed equal in LWM bridging or continued oral anticoagulation.

(ii) Thermal thrombus formation is still possible despite the use of open-irrigation but is markedly reduced in contrast to non-irrigated catheters.16 The use of advanced catheter-tip irrigation technology potentially reducing edge effects causing charring at the distal catheters shaft during radiofrequency energy delivery (CoolFlex, SJM) was not able to reduce silent embolism compared with all other 3.5 mm 8- to 12-hole open-irrigated catheters. Thermal thrombus formation at the tissue surface will possibly not be prevented by any irrigation technology and may be a cause of silent microemboli.

(iii) Air embolism through catheters and sheaths may have a significant role in the explanation of the variation of cerebral
embolism in different ablation methods. Especially, the introduction of bulky devices such as multielectrode, non-irrigated ablation catheters (pulmonary vein ablation catheter) carries a high risk of air embolism which is still evident in a lower proportion in conventional catheters. Careful catheter handling and avoidance of multiple catheter exchange may therefore be a crucial point in reducing the risk of silent microemboli.

(iiib) Microbubble formation has especially been shown in non-irrigated catheters or use of high-radiofrequency power. This source of silent embolism would possibly explain the similar rates of silent cerebral lesion in open-irrigated RFCA and cryoablation as similar rates of microembolic transcra\nnial signals have been reported for both methods. In addition, this mechanism could explain the huge differences to non-irrigated catheters that have been reported.

Comparison with previous publications

Energy source

The use of cryoablation catheters seems to create a similar amount of silent cerebral lesions when compared with open-irrigated tip catheters. In addition, Neumann et al. reported a similar risk for cryoablation vs. RFCA despite the fact that 38.6% of patients in the latter group had persistent AF and underwent additional linear lesions in 36.4% (vs. 0% in cryo). Therefore, the use of currently available alternative energy sources does not seem to be able to prevent all silent cerebral lesions. In contrast, the use of non-irrigated ablation devices should raise concerns about silent stroke risk: Sauren et al. reported a similar number of microembolic signals detected by transcranial Doppler sonography in RFCA with open-irrigated tip vs. cryoballoon ablation. However, significantly more microembolic signals were seen in RFCA without irrigation.

Risk factors

Neumann et al. reported that patients showing new cerebral lesions in MRI were significantly older (66 vs. 56 years in mean). This finding can be confirmed by our data revealing age as an independent risk factor in multivariate analysis.

The first study of Gaita et al. showed cardioversion during ablation to increase the risk of embolism 2.75-fold. We could not confirm this finding with the use of continued oral anticoagulation and a higher rate of electrical or medical cardioversion in our study group (34 vs. 27%). Our results might reflect a slight benefit of continued oral anticoagulation; however, a direct comparison would clearly be needed to confirm this observation. Another finding of Gaita et al. was the correlation of ACT with silent embolism showing a 17% risk in patients with an ACT <250 s and a 9% risk when ACT was >250. We could not see any correlation with ACT and were unable to create a cut-off value for an increased risk in our study. Only four patients of the whole population had minimum ACT values <250, only one patient had a mean value <250 and this patient in fact had a silent embolism. Of the patient group showing a positive finding in MRI, four (25%) had a minimum ACT of <300, only two (12.5%) had a mean ACT <300. Spontaneous echo contrast showed a trend to significance in the study of Gaita et al. (P = 0.074) and was an independent risk factor for silent stroke in our study population. Therefore, we suggest being extremely cautious in patients showing this finding in TEE and treating them accordingly with higher INR and ACT values.

CFAE ablation: There was a significant increase in the rate of embolism corresponding to the ablation technique performed with 5.4% for PVI only, 16% for additional linear lesions, and 32% for CFAE ablation. One factor might be the longer cumulative RF or procedure time, which would also be true for additional linear lesions. It is well possible that the small subgroups could not prove this true also for linear ablations. On the other hand also, the amount of ablated endocardial surface might be significantly larger in CFAE which may be another source of emboli by destructed endothelium. The value of CFAE ablation should therefore be critically reflected knowing that more than 80% of CFAE are no active sites, that the addition value on the success rate is questionable and that there is also a risk of later mechanical LA dysfunction.

Other studies concentrated on the difference between various energy sources (RFCA, cryo, or duty-cycled radiofrequency energy), which makes a comparison with our data difficult. Nonetheless, we can confirm the range of new silent embolism in the small RFCA subgroups.

Clinical relevance of subclinical cerebral embolic events after radiofrequency catheter ablation

All cerebral embolic events observed in our study were asymptomatic. Therefore, they would have remained unrecognized in everyday clinical practice. Even without previous RFCA, patients with AF have been reported to have an increased prevalence of silent cerebral infarctions on routine MRI monitoring compared with matched patients in sinus rhythm. It is well recognized that various cardiac interventions bare a substantial risk of apparent and silent stroke. As an example, the risk of stroke after transfemoral aortic valve implantation (TAVI) potentially due to the embolization of debris from the aortic root or from the calcified valve itself ranges between 0 and 10%. The rate of silent cerebral ischaemia in technically successful TAVI procedures has been reported to be up to 84% compared with an anyhow high 48% in open-valve surgery. Despite the very high number of multiple silent cerebral lesions, no apparent stroke was reported in this series in TAVI vs. one stroke (5%) in the open-surgery group. This rate of apparent vs. silent cerebral embolism also seems comparable with PVI procedures showing few clinical events.

Even diagnostic coronary angiography without intervention bares a similar risk of silent strokes as PVI in some patient groups. Kim et al. reported an incidence of 10.2% of new embolic lesions in MRI in vascular high-risk patients undergoing angiography before coronary artery bypass graft surgery. Interventional cardiac catherization showed similar rates of silent stroke (15%) in another manuscript, all of them asymptomatic.

Limitations

Our study represents a single-centre, non-randomized, but prospective study in a consecutive patient population undergoing AF ablation. The statistical power of this paper is limited. Still it is
the only study reporting data on the impact of continued oral anticoagulation on silent stroke risk in AF ablation. Larger, randomized studies using different techniques and anticoagulation regimes are needed.

We report acute data and follow-up data of the first 3 months after RFCA of AF. Therefore, we cannot conclude anything outside this time-range concerning evolution of cerebral lesions and especially about their influence on neurophysiological outcome.

The study lacks a control group with heparin bridging to eliminate confounders that could increase silent thromboembolism during LA ablation. It would be very difficult to compare two anticoagulation regimes in an institution like ours with patients on different wards used to stick to a single straight anticoagulation protocol. We can therefore only compare our data with similar studies using heparin bridging and reporting similar results with the use of open-irrigated tip catheters. We also cannot state any advantages or disadvantages of warfarin continuation over LMWH bridging.

The study as well lacks a control group undergoing cardioversion alone. Gaita et al. reported such a control group with zero percent silent embolisms whereas another working group published a 5% rate in patients after cardioversion. Therefore, we cannot exclude that cardioversion contributes to the risk of silent stroke which might be significant in larger study groups.

Neurophysiological outcome was not assessed in this study. Therefore, we cannot conclude anything on the long-term consequences of the silent cerebral lesions found in this study.

Conclusions

Radiofrequency ablation in patients under continued oral therapeutic anticoagulation is still associated with a substantial risk of silent embolism detected by cerebral MRI. Therefore, continuation of oral anticoagulation is not able to prevent cerebral embolism. A variety of different clinical and procedural factors contribute to the risk of cerebral lesions.

Conflict of interest: none declared.

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