Does periprocedural anticoagulation management of atrial fibrillation affect the prevalence of silent thromboembolic lesion detected by diffusion cerebral magnetic resonance imaging in patients undergoing radiofrequency atrial fibrillation ablation with open irrigated catheters? Results from a prospective multicenter study

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BACKGROUND Silent cerebral ischemia (SCI) has been reported in 14% of cases after catheter ablation of atrial fibrillation (AF) with radiofrequency (RF) energy and discontinuation of warfarin before AF ablation procedures.

OBJECTIVE The purpose of this study was to determine whether periprocedural anticoagulation management affects the incidence of SCI after RF ablation using an open irrigated catheter.

METHODS Consecutive patients undergoing RF ablation for AF without warfarin discontinuation and receiving heparin bolus before transseptal catheterization (group I, n = 146) were compared with a group of patients who had protocol deviation in terms of maintaining the therapeutic preprocedural international normalized ratio (patients with subtherapeutic INR) and/or failure to receive pretransseptal heparin bolus infusion and/or ≥2 consecutive ACT measurements <300 seconds (noncompliant population, group II, n = 134) and with a group of patients undergoing RF ablation with warfarin discontinuation bridged with low molecular weight heparin (group III, n = 148). All patients underwent preablation and postablation (within 48 hours) diffusion magnetic resonance imaging.

RESULTS SCI was detected in 2% of patients (3/146) in group I, 7% (10/134) in group II, and 14% (21/148) in group III ($P < .001$). "Therapeutic INR" was strongly associated with a lower prevalence of postprocedural silent cerebral ischemia (SCI). Multivariable analysis demonstrated nonparoxysmal AF (odds ratio 3.8, 95% confidence interval 1.5–9.7, $P = .005$) and noncompliance to protocol (odds ratio 2.8, 95% confidence interval 1.5–5.1, $P < .001$] to be significant predictors of ischemic events.

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CONCLUSION Strict adherence to an anticoagulation protocol significantly reduces the prevalence of SCI after catheter ablation of AF with RF energy.

KEYWORDS Atrial fibrillation; Ablation; Radiofrequency; Stroke; Silent cerebral ischemia; Warfarin; Periprocedural

ABBREVIATIONS **ACT** = activated clotting time; **AF** = atrial fibrillation; **CA** = catheter ablation; **CI** = confidence interval; **dMRI** = diffusion magnetic resonance imaging; **INR** = international normalized ratio; **IU** = international unit; **LA** = left atrium; **NPAF** = nonparoxysmal atrial fibrillation; **OR** = odds ratio; **PAF** = paroxysmal atrial fibrillation; **PV** = pulmonary vein; **RF** = radiofrequency; **RFCA** = radiofrequency catheter ablation; **SCI** = silent cerebral ischemia; **TIA** = transient ischemic attack

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Introduction

Atrial fibrillation (AF) is the most frequent supraventricular arrhythmia and has been associated with an increased risk of death, stroke, and hospitalization.[1–5] Radiofrequency (RF) catheter ablation (CA) has proven to be an effective treatment strategy for AF.[6] However, the ablation procedure itself is associated with a potential risk for iatrogenic periprocedural stroke.[6–10] Advancements in ablation catheters and strategies and improvements in periprocedural anticoagulation management have reduced such complications and have also improved the procedural success.[6–10] Nevertheless, because of the invasive and complex nature of CA, the incidence of thromboembolic events in ablation cases is still 1% to 5% (depending on ablation catheter used, anticoagulation strategy in the periprocedural period, and type of patients included in the study).[10,11]

In addition to stroke/transient ischemic attack (TIA), silent cerebral ischemia (SCI) represents an emerging complication of CA.[12] Therefore, stroke and TIA may represent only the tip of the iceberg.[7,8,10,11] Gaita et al[12] performed diffusion magnetic resonance imaging (dMRI) before and after RFCA. They demonstrated that SCI was more prevalent than clinical periprocedural thromboembolic events, reporting a SCI prevalence of up to 14%. Furthermore, a significant correlation between SCI and reduced cognitive performance has recently been reported.[13] Although the effects of symptomatic stroke are notably dramatic for patients, SCI also is worrisome because it significantly increases the likelihood of further cerebral damage in a patient population that already is at higher risk for cerebral embolism and dementia.[5,14] This implication is notable for physicians because patients undergoing RFCA procedures will undergo repeat ablations in 30% to 50% of cases, raising the possibility for cumulative damage.[15] The energy source and ablation technology used seem to influence the prevalence of SCI, which is as high as 38% in some cases.[12,16–22]

Periprocedural thromboembolic complications potentially could be prevented by making adjustments to the management of anticoagulation before and after CA.[10,11] At present, data on treatment of SCI using any energy source or technology have been reported for periprocedural anticoagulation management that includes warfarin discontinuation before the procedure and a "bridge" with low molecular weight heparin 3 to 5 days before the procedure and then restart with warfarin after the procedure.[12,16–22] The role of periprocedural anticoagulation management in SCI prevention has not been widely investigated. Because stroke and TIA rates during AF ablation have been dramatically reduced with the performance of CA for AF without warfarin discontinuation,[10,11] we sought to assess whether strict periprocedural anticoagulation management could affect the prevalence of SCI after RFCA using open irrigated catheters.

Methods

Consecutive patients undergoing RFCA for symptomatic and drug-refractory AF and under "therapeutic" warfarin were included in this prospective multicenter study. All patients included in the study were matched with a control population of consecutive patients undergoing RFCA in the same time period at each enrolling institution but with warfarin discontinuation before CA that was bridged with low molecular weight heparin.[10] Anticoagulation treatment before ablation was decided by the treating electrophysiologist based on his or her preference. The definitions of AF followed those of the American Heart Association and the Heart Rhythm Society.[23]

All patients underwent preablation and postablation (within 48 hours) dMRI. Exclusion criteria were age <18 years or >80 years, valvular heart disease with surgical indication, acute coronary syndrome <3 months, or other contraindications to dMRI. All patients provided written informed consent. The study was approved by the Institutional Review Board of each institution.

Periprocedural anticoagulation management

Patients undergoing ablation without warfarin discontinuation (on warfarin)

Warfarin was initiated 4-6 weeks before the ablation procedure, and a "therapeutic international normalized ratio (INR) range" for 4 weeks before the procedure was requested. Warfarin was not stopped the night before the procedure and was taken the night of the procedure. Transesophageal echocardiography was performed only in patients without sinus rhythm the day of the procedure and if they presented to the electrophysiology laboratory with a subtherapeutic INR on the day of procedure. Patients with a subtherapeutic INR on the day of the procedure were included in the study. If INR was >3.5, patients were given 1 to 2 units of fresh frozen plasma before the procedure.

Before transseptal catheterization puncture, an intravenous bolus of heparin 10,000 international units (IU) was administered in males and 8000 IU in females irrespective of body weight. During the procedure, activated clotting time (ACT) was checked every 20 minutes, and additional heparin boluses were administered as needed to maintain ACT >300 seconds. The transseptal sheaths were continuously infused with heparinized saline (2000 IU per 250-mL bag) during the entire procedure. RF energy was delivered with a 3.5-mm open irrigated ablation catheter (Biosense Webster, Baldwin Park, CA) with a maximum temperature of 42°C, power up to 45 W, and flow rate of 30 cc/min with heparinized fluids.

After ablation was completed in the left atrium (LA), heparin was partially reversed with protamine guided by the ACT values. Sheaths were removed when ACT was <200 seconds. In case of perforation with cardiac tamponade, heparin was stopped and reversed with protamine. Fresh frozen plasma was used to reverse the warfarin effect.

Patients undergoing ablation with warfarin discontinuation (off warfarin)

Warfarin was initiated 4-6 weeks before the ablation procedure, and a "therapeutic INR range" for 4 weeks before the procedure was requested. Warfarin was discontinued 3 days before the ablation procedure, and enoxaparin 0.5 mg/kg was administered until 12 hours before the procedure twice per day. An intravenous bolus of heparin of 15000 IU was given before the transseptal puncture. A continuous infusion of heparin 1000 U/h was started. The infusion was adjusted to maintain ACT >300 seconds.

All patients underwent transesophageal echocardiography before ablation to rule out the presence of LA thrombus. At the end of the procedure, protamine was given to partially reverse the heparin effect. Warfarin was restarted the evening of the procedure. In addition, enoxaparin 0.5 mg/kg bid was routinely started about 3 hours after the sheaths were removed and was stopped when the INR reached a "therapeutic range." During the procedure, ACT was checked every 20 minutes, and additional heparin boluses were administered as needed to maintain ACT >300 seconds. The transseptal sheaths were continuously infused with heparinized saline (2000 IU per 250-mL bag) during the entire procedure. RF energy was delivered with a 3.5-mm open irrigated ablation catheter (Biosense Webster) with a maximum temperature of 42°C, power up to 45 W, and flow rate of 30 cc/min with heparinized fluids. Sheaths were removed when ACT was <200 seconds. In case of perforation with cardiac tamponade, heparin was stopped and reversed with protamine.

Electrophysiologic study and ablation procedure

Our approach has been described in detail elsewhere.[12,23–25] Briefly, antiarrhythmic drugs were discontinued 4 to 5 half-lives before ablation. A double transseptal access was performed in all patients. A circular mapping catheter (Lasso, Biosense Webster) was used to guide the ablation together with intracardiac echocardiography, and a 3.5-mm open irrigation tip catheter (ThermoCool, Biosense Webster) were used for ablation. In all patients with paroxysmal atrial fibrillation (PAF), pulmonary vein (PV) antrum isolation was performed. Isolation of the PV antrum could be extended to the posterior wall. The superior vena cava also was isolated if PV-like potentials were recorded in that region. In patients with nonparoxysmal atrial fibrillation (NPAF), electrical isolation of the PV antrum was extended to the entire posterior wall down to the coronary sinus and to the left part of the septum. Complex fractionated atrial electrograms were ablated as well. The LA appendage and coronary sinus could be isolated when deemed to be necessary. After ablation, isoproterenol challenge (up to 30 μg/min) was performed to reveal non-PV triggers or to exclude the presence of PV reconnection. Non-PV triggers were defined as any sustained and nonsustained firing sites outside the PVs.

dMRI

All patients underwent preablation and postablation (within 48 hours) dMRI. Radiologists who read the MRI scans were blinded to anticoagulation status. The MRI protocol used has been described in detail elsewhere.[12,13] In brief, images at each different site were obtained using 1.5-T clinical MRI (GE Healthcare, Waukesha, WI, and Siemens Vision Plus, Erlangen, Germany) scanners according to standard protocols. These protocols contained (1) T1 sagittal, (2) DWI axial, (3) flair axial, (4) T2 axial, (5) T1 axial, (6) T2* coronal, and (7) GRE-EPI coronal images as needed to delineate acute lesions within 48 hours compared to preablation scans. Neuroanatomic localization and characteristics were assessed and recorded, separating acute infarct and hemorrhages from unaffected subjects.

Statistical analysis

Continuous data are reported as mean ± SD or as count and percent if categorical. The Student *t* test, one-way analysis of variance, χ^2 test, and Fisher exact test were used to compare differences across groups. Univariate and multivariate logistic regression was used for identifying independent predictors of silent thromboembolic stroke. Potential confounders entered into the multivariable model were identified based on known clinical relevance or significant association observed in univariate analysis. The controlling variables used in the model were age, gender, LA diameter, $CHADS_2$ score, and AF type. Tests were run to determine the presence of multicolinearity of the covariates. Odds ratio (OR) and 95% confidence interval (CI) of SCI were computed. All tests were 2-sided, and $P < .05$ was considered significant. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

A total of 280 consecutive patients undergoing CA for AF on warfarin and a matched control population of 148 patients (group III patients) undergoing RF ablation off warfarin were

Table 1 Baseline characteristics

	Group I (n = 146)	Group II (noncompliant, n = 134)	Group III (n = 148)	*P* value
Male	114 (78)	105 (78)	115 (78)	1
Age (years)	59 ± 9	58 ± 9	58 ± 10	.58
Atrial fibrillation type				
Paroxysmal	38 (26)	40 (30)	55 (37)	.11
Persistent	47 (32)	42 (31)	50 (34)	1
Long-standing persistent	61 (42)	54 (40)	46 (31)	.14
Cardioversion	38 (26)	24 (18)	40 (27)	.15
ACT during procedure (seconds)	362 ± 35	356 ± 42	348 ± 64	.08
$CHADS_2$ score ≥2	28 (19)	24 (18)	20 (14)	.39
Left ventricular ejection fraction (%)	58 ± 8	58 ± 11	60 ± 10	.13
Left atrial diameter (cm)	4.6 ± 0.7	4.4 ± 0.7	4.3 ± 0.8	<.01
Coronary artery disease	31 (21)	21 (16)	24 (16)	.41
Hypertension	69 (47)	54 (40)	58 (39)	.32
Dyslipidemia	35 (24)	29 (22)	28 (19)	.58
Body mass index	29 ± 6	29 ± 6	29 ± 5	.40
Congestive heart failure	7 (5)	8 (6)	4 (3)	.39
Diabetes	32 (22)	28 (21)	40 (27)	.42

Values are given as no. (%) or mean ± SD. ACT = Activated clotting time.

included in the study. Of the 280 patients on warfarin, 146 maintained a therapeutic INR, received heparin bolus before transseptal catheterization, and all had ACT >300 seconds (group I patients, compliant to protocol group), whereas 134 had an anticoagulation protocol deviation: failed to maintain a therapeutic preprocedural INR, had a subtherapeutic INR, and/or failed to receive pretransseptal heparin bolus infusion or had at least 2 consecutive ACT <300 seconds (group II, noncompliant population). Baseline characteristics of the 3 groups did not show any statistical difference and are summarized in Table 1.

Procedural results

Sixty-two percent of patients (n = 91) in group I , 64% in group II (n = 86), and 54% (n = 80) in group III entered the electrophysiology laboratory in AF/atrial tachycardia (P = .18). Persistence of AF/atrial tachycardia at the end of the procedure was observed in 38 patients (26%) in group I, 24 patients (18%) in group II, and 40 patients (27%) in group III (P = .15). Sinus rhythm was achieved in these patients by electrical cardioversion.

Mean procedural time was 165 ± 62 minutes, 157 ± 56 minutes, and 152 ± 48 minutes (P = .16) and RF ablation times were 78 ± 32 minutes, 75 ± 30 minutes, and 69 ± 35 minutes (P = .12) for groups I, II, and III, respectively.

Clinical TIA/stroke

A periprocedural symptomatic TIA occurred in a group II patient with long-standing persistent AF and subtherapeutic INR of 1.6 on the day of the procedure. Two periprocedural strokes occurred in group III patients and both had long-standing persistent AF and $CHADS_2$ score of 3 and 4, respectively. No TIA/strokes occurred in group I patients.

Preablation SCI

SCI preablation did not differ among groups: 44% positive SCI in group I, 42% in group II, and 43% in group III (P = .94).

Postablation SCI

SCI at postprocedure dMRI was detected in 2% (3/146) in group I, 7% (10/134) in group II, and 14% (21/148) in group III (P <.001). Figure 1 shows the results sorted by rhythm on the day of the procedure. The 3 patients in group I had small single lesions with diameters of 2.5 mm, 3 mm, and 4 mm (Figure 2). The group II patients had lesions that also were single and ranged in diameter from a minimum of 4 mm up to 8 mm (Figure 3). The incidence of SCI in group III patients was significantly higher than in groups I and II (P <.001 and P <.04, respectively), with 2 lesions that reached approximately 30 mm in diameter and 5 patients (4%) who reported multiple (2-3) lesions (Figure 4).

Predictors of SCI

Risk of SCI according to baseline risk factors was assessed using a univariate logistic model. AF type (OR 3.9, 95% CI 1.64–9.36, P = .002) and subtherapeutic INR before the

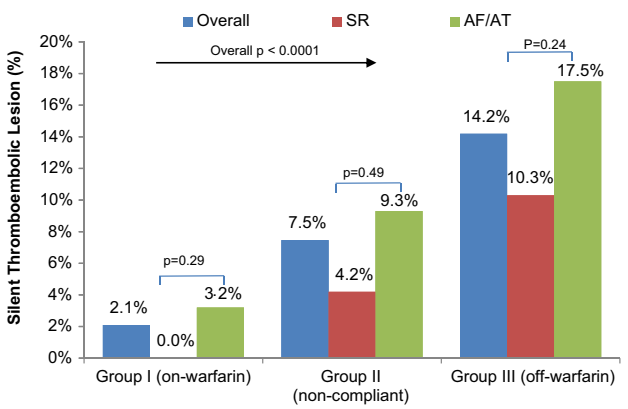

Figure 1 Incidence of silent cerebral ischemia in the 3 groups sorted by rhythm on the day of the procedure. AF = atrial fibrillation; AT = atrial tachycardia; SR = sinus rhythm.

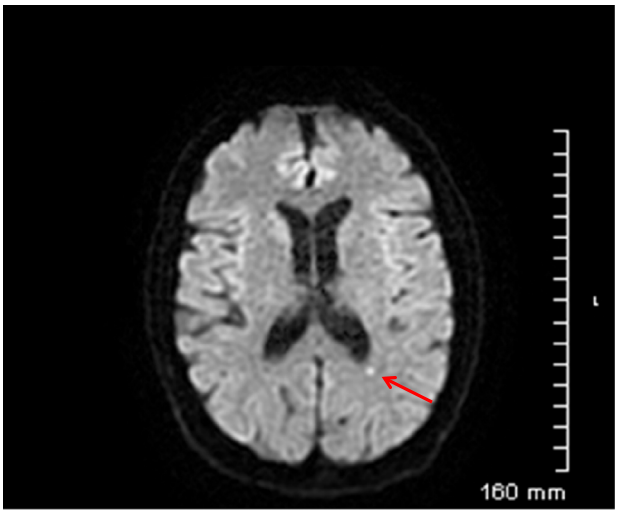

Figure 2 Positive diffusion magnetic resonance imaging *(red arrow)* showing a single lesion <5 mm in diameter in a group I patient with nonparoxysmal atrial fibrillation.

procedure (OR 3.1, 95% CI 1.45–10.2, $P = .006$) showed strong prognostic association with SCI. In addition, noncompliance with the specified periprocedural anticoagulation protocol with the targeted ACT level demonstrated higher risk for SCI. ACT <300 seconds (observed on at least 2 consecutive measurements) during the procedure and no administration of heparin bolus before transseptal catheterization had univariate OR of 3.2 ($P = .005$) and 1.6 ($P = .01$), respectively. However, no association was seen between LA time and SCI in the overall population (OR 1.003, 95% CI 0.96–1.01, $P = .36$). When examining the population off warfarin, LA time demonstrated significant association (OR 1.05, 95% CI 1.004–1.07, $P = .028$). Results from the univariate analysis are given in Table 2.

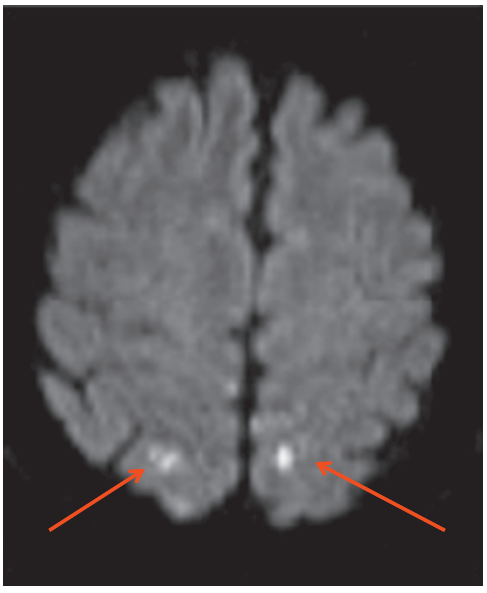

Figure 4 Bilateral parietal embolic lacunar infarct *(red arrows)* in a group III patient. Both lesions appear to be >5 mm in diameter.

Multivariate analysis was performed using the logistic regression model (model 1). The significant confounders identified in the univariate test were included in the model. After adjusting for the confounders, subtherapeutic INR and ACT <300 seconds during the procedure were strongly associated with postprocedural SCI (OR 2.8, 95% CI 1.5–5.1, $P < .001$, and OR 1.8, 95% CI 1.2–2.68, $P = .003$, respectively). Furthermore, multivariable analysis revealed that NPAF independently predicted SCI (OR 3.8, 95% CI 1.5–9.7, $P = .005$), and cardioversion did not show any significant association at either the univariate (OR 1.04, 95% CI 0.89–1.03, $P = .371$) or multivariate level (OR 2.1, 95% CI 0.6–7.2, $P = .244$). In group I patients, all 3 events

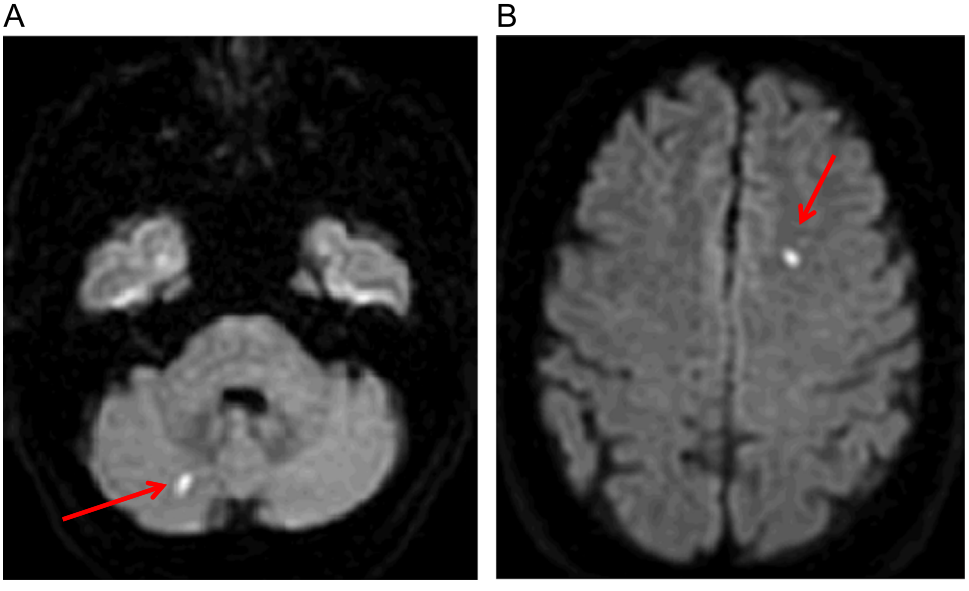

Figure 3 Positive diffusion magnetic resonance imaging *(red arrow)* in two group II patients who were noncompliant to protocol. Lesions appear to be single small embolic lacunar infarcts. No bleeds or cortical infarcts are seen.

Table 2 Univariate association of baseline risk factors with silent ischemic attack

	Odds ratio	95% Confidence interval	*P* value
Age (years)	1.01	0.95–1.07	.753
Gender (female)	1.11	0.99–1.03	.271
Atrial fibrillation type	3.923	1.64–9.36	.002
Cardioversion	1.04	0.89–1.03	.371
Hypertension	0.998	0.95–1.05	.939
Body mass index	1.07	0.96–1.18	.225
Diabetes	1.38	0.95–1.78	.12
$CHADS_2$ score	1.32	0.87–2.63	.27
Left ventricular ejection fraction (%)	0.977	0.91–1.05	.535
Left atrial diameter (cm)	0.998	0.96–1.04	.939
Subtherapeutic international normalized ratio	3.088	1.45–10.02	.006
Activated clotting time <300 seconds	3.2	1.26–4.5	.005
Left atrial time (minutes)	1.003	0.96–1.01	.36
No heparin bolus before transseptal catheterization	1.63	1.16–2.3	.011

(100%) occurred in the non-PAF population, whereas in group III patients (off warfarin), 62% of events were reported in those with PAF and 38% in those with persistent AF.

Discussion

Main findings

This is the first large prospective study that sought to detect SCI assessed by dMRI after RFCA of AF using an open irrigated catheter while on uninterrupted warfarin with a "therapeutic" INR. We showed that performing CA with "therapeutic INR" and strict adherence to an anticoagulation protocol that includes pretransseptal catheterization intravenous heparin bolus and ACT >300 seconds significantly reduces the prevalence of SCI compared to patients off warfarin and those noncompliant with the anticoagulation protocol. In addition, SCI occurred predominantly in patients with long-standing persistent AF in whom extensive LA ablation was performed. Of note is the finding that SCI did not correlate with electrical cardioversion.

Another important finding is that all lesions that occurred in the group on warfarin were single and had a diameter <5 mm. Considering the potential cumulative damage of SCI due to repeat procedures, especially in NPAF patients,[15] the drastic reduction of SCI obtained with therapeutic INR appears to be of utmost importance even though no link between SCI and neurocognitive function has yet been proven.

Schwarz et al[26] found no correlation between cognitive decline and MRI-detected acute brain lesions after ablation. Similarly, Herm et al[27] observed no significant alteration in attention and executive functions, memory, and learning at 6-month follow-up in a prospective trial with long-term follow-up MRI data. In contrast, Gaita et al[13] recently showed that patients with AF and positive asymptomatic findings at MRI have a worse cognitive performance compared to patients in sinus rhythm. Therefore, the results of our study showing a significant reduction of SCI could be clinically relevant, although this study was not designed to address this issue.

Possible explanation of our findings compared with previous studies can be summarized as follows. In all previous studies, warfarin was discontinued before ablation, thus modifying its protective effect. This is clearly shown by the fact that subtherapeutic INR on the day of the procedure increased SCI prevalence from 2% to 7 %. Full-dose heparin bolus administration before transseptal catheterization is another relevant issue. As shown in 2005 by Tse et al,[28] heparin has an important role in preventing or blocking platelet activation, which occurs immediately after sheaths are inserted into the body. Warfarin has no role in preventing or blocking platelet activation. We showed that in up to 9% of patients either on or off warfarin, thrombus on the sheath in the right atrium, visualized by intracardiac echocardiography, was present before transseptal catheterization.[29] Following the observations of Gaita et al[12] on the prevalence of SCI in patients who had undergone CA with RF energy, SCI has been reported with use of different energy sources and different technologies. SCI have been detected in 8% to 41% of all patients after CA.[16,18,30,31] For all published data, the common method of periprocedural anticoagulation was discontinuation of warfarin and bridge with low molecular weight heparin.[12,16–22]

This is the first study assessing the prevalence of SCI in patients who were kept on therapeutic warfarin and adhered to a strict anticoagulation protocol. The study clearly showed no occurrences of symptomatic stroke in patients who were kept on warfarin. In their pilot study, Gaita et al[12] concluded that the incidence of SCI was heavily correlated with cardioversion during the ablation procedure. In contrast, the present study shows that a strict anticoagulation protocol and not cardioversion significantly reduces the occurrence of SCI. Notably, many of our patients were NPAF and had undergone extensive LA ablation.

Several other considerations should be taken into account when comparing the 3 groups in this study. The baseline characteristics of the patients and procedural parameters were similar among groups (e.g., AF type, previous stroke, arrhythmia duration, thrombotic predisposition, number of RF lesions, LA procedural time), so no confounding factors biased our results. During the procedures, several

measurements of ACT were <300 seconds in groups II and III but never in group I. This might have played an important role that is attributable to the "therapeutic" warfarin effect. Management of sheaths and foreign bodies was similar among groups. Although a significant reduction of SCI was observed in group I, the role of air embolism determining SCI is still controversial.

Predictors for SCI

Recent studies have identified ACT,[12,19] intraprocedural electrical cardioversion,[12,19] preablation transesophageal echo contrast,[16] and extensive LA ablation of complex fractionated atrial electrograms and other structures as independent predictors of SCI. Although data on all of these variables are controversial, our study, which includes many patients with NPAF, provides some insight into the issue of SCI.[12,16,18,31,32]

Recent animal studies have indicated that MRI-detected SCI are the results of cerebral ischemic lesions and lead to glial scarring. These lesions may not be appropriately detected using current MRI technology.[33,34] The fact that many of these lesions regress over time may be due to a limitation in current diffusion MRI techniques and does not necessarily reflect their disappearance. Haines et al[33,34] showed in an animal study that SCI usually resolves on MRI within 4 days after occurrence despite the presence of permanent brain lesions at pathologic examination. Whether smaller and larger SCI represent different mechanisms (air embolism vs thrombotic embolism) requires further evaluation.

Study limitations

The main limitation of our study is the absence of formal randomization. Although we acknowledge this limitation, all of the study data were collected in a prospective fashion, and all procedures were performed in the same time period, thus eliminating confounding factors such as operator experience and technology advancements. Another limitation of the study is that RF energy was the only ablation energy source tested in this study. MRI were not interpreted using a core laboratory. Finally, no neurocognitive tests were performed before and after ablation.

Conclusion

This study shows that when RFCA of AF is performed under "therapeutic" warfarin with strict adherence to an anticoagulation protocol, the prevalence of SCI is significantly reduced. The risk of SCI appears to be limited to patients with long-standing persistent AF in whom extensive LA ablation was performed. Importantly, all lesions were small (< 5 mm) and always were single.

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