Evaluation and Reduction of Asymptomatic Cerebral Embolism in Ablation of Atrial Fibrillation, But High Prevalence of Chronic Silent Infarction

Results of the Evaluation of Reduction of Asymptomatic Cerebral Embolism Trial

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Methods and Results—Sixty subjects (age 60±10 years; 87% paroxysmal; CHADS2 score, 0.6±0.7) undergoing AF ablation with a circular MER catheter were studied. Three procedural changes were specified: (1) ablation was performed under therapeutic vitamin K antagonist and heparin to maintain activated clotting time >350 seconds; (2) submerged loading of the catheter into the introducer before sheath insertion to minimize air ingress; and (3) either the distal or proximal electrode of the circular MER catheter was deactivated to prevent inadvertent bipolar radiofrequency interaction. MRI was performed <7 days preablation and 2 days postablation. Subjects with new cerebral findings after ablation underwent repeat MRI after 1 month. An acute ACE lesion was defined by a new hyperintensity on diffusion-weighted and fluid-attenuated inversion recovery cerebral MRI sequences. Neurological function was evaluated at baseline, postablation, and 1 month. All target pulmonary veins were isolated. In 60% (36/60) of patients, pre-existing cerebral lesions were seen on the preprocedure MRI (8 lesions per subject; interquartile range, 3–22). New postprocedural ACE occurred in only 1/60 patients (incidence, 1.7%; 95% confidence interval, 0.04–8.9), which was no longer visible on MRI after 1 month.

Conclusions—Applying procedural changes to MER ablation significantly reduces the ACE incidence to 1.7%, which is on the low end of reported ACE rates of any technology.

Clinical Trial Registration Information—ClinicalTrials.gov; Identifier: NCT01520532.

Key Words: atrial fibrillation ▪ catheter ablation ▪ cerebral infarction ▪ clinical trial ▪ embolism

Pulmonary vein (PV) isolation is an effective therapy to alleviate symptoms and restore sinus rhythm in patients with atrial fibrillation (AF).1 However, recent reports have shown that ablation in the left atrium (LA) is associated with new asymptomatic cerebral emboli (ACE) visible on postprocedural diffusion-weighted cerebral MRI.2 The largest such study reported an ACE incidence of 14.2% using open-irrigation radiofrequency (RF) catheters.3 Although no patient parameters were correlated with ACE, procedural parameters, such as cardioversion and activated clotting time (ACT) level, were associated with new silent lesions. Smaller subsequent reports with rates ranging from 7% to 12% have similarly implicated procedural factors to increasing ACE incidence, including concomitant diagnostic coronary angiography,4 total RF duration,5 and non-PV ablation.6

Two nonrandomized studies found that use of multielectrode RF (MER) ablation was associated with elevated ACE incidence compared with irrigated RF and cryoablation, with a rate as high as 38%.7,8 Subsequent animal studies showed that both gaseous and solid emboli were generated during both irrigated and MER ablation in the swine LA.9 Specifically with the circular MER catheter, increased gas emboli were observed during catheter insertion into transeptal sheaths while both embolic and gaseous
particles were observed when activated electrodes were provocatively overlapped during ablation. These gaseous and solid emboli were found to be the cause of cerebral embolic MRI findings in animal models similar to those seen in humans. Thus, the aim of this study was to establish if ACE incidence in patients could be reduced by applying specific procedural techniques identified in the preclinical setting to reduce the embolic load.

Methods

Patient Population
The study population consisted of 68 subjects enrolled at 1 Canadian and 6 European centers, all experienced with the circular MER ablation system. To be eligible for the study, patients had to be >18 years of age and had symptomatic AF indicated for catheter ablation. Exclusion criteria included prior AF ablation, recent history of cerebral vascular accident (<6 months), contraindication to MRI, contraindication to vitamin K antagonism (VKA), active LA thrombus, ablation with nonstudies devices, and pregnancy. The study was approved by each center’s ethics review board and all patients gave written informed consent before study inclusion. The study was registered on ClinicalTrials.gov; NCT01520532. Eight subjects were excluded from analysis after enrollment. Seven of the 8 exclusions did not undergo a study ablation procedure because of very subtherapeutic international normalized ratio (INR) on the day of procedure (n=3), use of a different ablation technology (n=1), prior LA ablation (n=1), inability to cross the septum (n=1), and withdrawal of study consent (n=1). One of the 8 exclusions underwent ablation but did not undergo a postprocedure MRI.

Study Design

The Evaluation of Reduction of Asymptomatic Cerebral Embolism (ERACE) trial was a prospective, multicenter, cohort study intended to assess the acute clinical impact of applying specific procedural changes, as compared with previous studies using MER technology, including: (1) performing the procedure on therapeutic, uninterrupted oral VKA with INR ≥2.0 and intraprocedural heparin to keep ACT >350 seconds; (2) loading the catheter into the introducer submerged in saline before sheath insertion to reduce air ingress; and (3) deactivation of either the distal or proximal electrode on the MER catheter to avoid electrode overlap and phased RF interaction. These changes were derived from preclinical investigations into embolic load creation. Protocol-defined subject evaluations were conducted preprocedure, immediately postprocedure, and 1 month postprocedure. All visits included a medical history, physical examination with neurological assessment, and protocol-specified cerebral MRI evaluations as detailed below.

Periprocedural Anticoagulation

Administration of oral anticoagulation with VKA to achieve an INR ≥2.0 was initiated 24 weeks before the ablation procedure. Oral anticoagulation was maintained throughout the ablation procedure without interruption or bridging and for the duration of follow-up. Patients were targeted to have an INR ≥2.0 on the day of ablation. Novel oral anticoagulants were excluded from this study, including dabigatran, rivaroxaban, and apixaban. Within 24 hours of ablation, patients also underwent transesophageal echocardiography to rule out LA thrombus. A single transseptal puncture was performed and the MER catheter was inserted into the LA using a steerable sheath (n=25; 10 French Channel [Bard Electrophysiology, Lowell, MA]; or 10 French Flexcath [Medtronic, Minneapolis, MN]) or nonsteerable sheath (n=35; 10 French SL-1 [St Jude Medical, Minneapolis, MN]; or 10 French Arrive [Medtronic]). Intravenous unfractionated heparin was administered just before or immediately after transseptal puncture and maintained throughout the ablation procedure to keep the ACT ≥350 seconds. The first RF application was not permitted by protocol until a documented ACT ≥350 seconds was achieved. If the ACT fell <350 seconds during the case, investigators were asked to give an additional bolus of heparin and repeat the ACT immediately afterward. Otherwise, ACTs were monitored every 15 minutes.

Ablation Protocol and Procedural Techniques

The ablation system consisting of a multichannel RF generator and a circular MER ablation catheter (GENius Generator and Pulmonary Vein Ablation Catheter; Medtronic Ablation Frontiers, Carlsbad, CA) has been previously described. Briefly, the circular MER catheter delivers duty-cycled, phased RF energy via the generator to the PV antrum. Phase-shifted energy delivery between adjacent catheter electrodes (bipolar) and return electrodes (unipolar) allows creation of long, contiguous lesions with each RF application. Increasing the ratio of unipolar-to-bipolar energy allows an increase in lesion depth. RF is delivered in temperature-controlled and power-limited fashion (60°C; 10 W) with typical duration of 60 seconds. Energized electrodes with low power (<3 W) or low temperature (<50°C) were deselected during ablation to minimize ineffective RF delivery. All PVs were isolated using the circular MER catheter by multiple applications of phased RF delivery around each of the PV antra identified by contrast fluoroscopy, intracardiac echography, or preprocedural imaging. Two centers used intracardiac echocardiography routinely (10 French Acuson; Siemens, Erlangen, Germany) and the catheter was kept in the right atrium and was not introduced into the LA. The procedural end point of PV isolation entrance block was assessed via signal interpretation using the circular MER catheter and pacing maneuvers from the PV, coronary sinus, or LA where appropriate. Adenosine or isoproterenol provocation was not systematically performed. To allow for verification of PV isolation, sinus rhythm was restored by direct current cardioversion at the end of procedure, when needed.

To reduce air entrapment around the array, and inadvertent introduction of air into the transseptal sheath and LA, the distal end of the circular MER catheter was submerged and captured by the introduction device in a saline bath immediately before sheath insertion (Figure 1). Transseptal sheaths were also aspirated and flushed with heparinized saline before and after catheter introduction to avoid air ingress. The sheaths were also either periodically or continuously flushed during the ablation procedure with heparinized saline to prevent embolus formation as per each center’s practice. Investigators were also asked to avoid any catheter exchanges through the transseptal sheath; both ablation and pacing maneuvers were performed with the same MER catheter without exchanging for other diagnostic/pacing catheters in the LA.

Finally, to eliminate the possibility of distal and proximal electrode overlap with resulting bipolar electrode electrical interaction (Figure 2), either the distal or proximal electrode was always deactivated before RF delivery.

Cerebral MRI and Neurological Assessments

Cerebral MRI was performed using a 1.5-T scanner (Signa HDxt; GE Healthcare, Milwaukee, WI; Intera/Achieva; Philips, Eindhoven, the Netherlands; or Avanto/Symphony; Siemens) using the same standardized acquisition protocol, which has been described previously.
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Cerebral MRI scans were performed <7 days preablation and 24 to 48 hours postablation in all subjects. For patients with a new postprocedure finding, the cerebral MRI was repeated at the 1-month visit. The ACE definition used in this trial was identical to that previously described by Gaita et al. Briefly, postprocedural ACE lesions were defined by any new focal hyperintensities detected on the postablation T2–fluid-attenuated inversion recovery images corresponding to restricted diffusion on the diffusion-weighted sequences. Pre-existing lesions (PELs) on cerebral MRI were defined as focal hyperintense areas detected by the T2–fluid-attenuated inversion recovery sequence on the preablation MRI. The number and size of both pre-existing and new cerebral lesions were recorded. All acquired MRIs were sent to a core laboratory and were interpreted by 2 independent, blinded neuroradiologist reviewers. In cases of disagreement, reviewers reached a consensus before final adjudication.

All subjects underwent neurological assessment at each study visit with the Mini-Mental State Exam (MMSE) and the National Institutes of Health (NIH) Stroke Scale. Details of these scales are provided in the online-only Data Supplement (eMethods 2).

Study End Points

The primary end point was incidence of new ACE lesions on postprocedure cerebral MRI. Secondary endpoints included assessment of preablation lesions on MRI; all serious adverse events that were related, or probably related, to the procedure or ablation system; the ability to achieve the end point of PV isolation with the study system; and any new abnormal findings on neurological assessment.

Statistical Analysis

Demographics, medical history, and other clinically relevant variables are summarized using descriptive statistics, including mean±SD, median, range for continuous variables, and percentages for qualitative variables. Comparisons were performed using Pearson χ² test for categorical variables and the Student t test for parametric or nonparametric continuous variables, respectively. Binomial confidence intervals (95%) were calculated using the Clopper–Pearson method. Repeated measures analysis of variance models were used to compare changes in neurological scores from baseline for all patients and among patients with and without PEL across study visits. Relationship between pre-existing MRI lesions and CHA2DS2-VASc score was performed by linear regression. A P value of <0.05 was considered statistically significant. Statistical analyses were conducted with IBM SPSS Statistics 20 (IBM, Armonk, NY).

Results

Patient Characteristics

From March to October 2012, 60 subjects completed all scheduled study visits and assessments, with baseline characteristics detailed in Table 1. The study population had a mean age of 60 ± 10 years and modest left atrial enlargement (42 ± 5 mm).

Table 1. Baseline Subject Demographics

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>All Subjects (N=60)</th>
<th>No PEL (n=24)</th>
<th>PEL (n=36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.3±9.7</td>
<td>57.0±9.0</td>
<td>62.6±9.6</td>
<td>0.028</td>
</tr>
<tr>
<td>Gender, % men</td>
<td>68%</td>
<td>75%</td>
<td>64%</td>
<td>0.41</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>48%</td>
<td>29%</td>
<td>61%</td>
<td>0.015</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>3%</td>
<td>0%</td>
<td>6%</td>
<td>0.51</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>7%</td>
<td>0%</td>
<td>11%</td>
<td>0.091</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>...</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>0.6±0.7</td>
<td>0.4±0.6</td>
<td>0.8±0.7</td>
<td>0.032</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>1.3±1.2</td>
<td>0.8±1.1</td>
<td>1.6±1.2</td>
<td>0.0063</td>
</tr>
<tr>
<td>History of AF, y</td>
<td>4.5±4.9</td>
<td>4.0±5.1</td>
<td>4.9±4.8</td>
<td>0.51</td>
</tr>
<tr>
<td>Episodes of AF in the past 3 mo (no. of subjects ≥10)</td>
<td>22 (37%)</td>
<td>7 (30%)</td>
<td>15 (43%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Prior cardioversion in last 12 mo, % yes</td>
<td>24 (40%)</td>
<td>9 (38%)</td>
<td>15 (42%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Persistent AF, %</td>
<td>8 (13%)</td>
<td>4 (14%)</td>
<td>7 (19%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospitalizations for AF, before 12 mo</td>
<td>1.1±1.3</td>
<td>1.1±1.3</td>
<td>0.7±0.9</td>
<td>0.17</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>41.6±4.9</td>
<td>39.4±4.2</td>
<td>42.9±4.8</td>
<td>0.020</td>
</tr>
<tr>
<td>National Institutes of Health Stroke Scale score</td>
<td>0.20±0.61</td>
<td>0.33±0.82</td>
<td>0.11±0.40</td>
<td>0.23</td>
</tr>
<tr>
<td>Mini-Mental State Exam score</td>
<td>28.8±1.8</td>
<td>28.5±2.4</td>
<td>28.9±1.2</td>
<td>0.36</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; and PEL, pre-existing lesion.
The majority of patients had paroxysmal AF (n=52), whereas a small number had persistent AF (n=8). None of the patients had long-standing persistent AF. They were at low risk for symptomatic thromboembolism (CHADS2, 0.6±0.7; CHA2DS2-VASc, 1.3±1.2). Patients had previously tried and failed flecainide (n=25), sotalol (n=19), propafenone (n=6), amiodarone (n=5), and dronedarone (n=14) before the ablation procedure.

Pre-Existing Cerebral MRI Lesions

The prevalence of subjects with PELs on preprocedure MRI was 60% (36/60), with a burden of 8 lesions per subject (interquartile range [IQR], 3–22; Figure 3). PEL had median volume of 166 mm³ (IQR, 52–636). Lesions were predominantly in the white matter (99%). PELs were distributed in the frontal (56%), parietal (25%), insular (6.2%), subinsular (4.3%), temporal (3.2%), limbic (3.1%), and occipital (2.2%) lobes. Patients with PELs were older (P=0.03), more likely to have hypertension (P=0.01), had larger left atrial diameter (P=0.02), and had higher CHADS2 (P=0.03) and CHA2DS2-VASc scores (P=0.006; Table 1). Median number of lesions per patient by CHA2DS2-VASc score were: 0 (IQR, 0–2.5) for score 0; 3 (IQR, 0–6) for score 1; 2 (IQR, 1–17) for score 2; 23 (IQR, 0–37) for score 3; and 6.5 (IQR, 5–8) for score 4. By linear regression, there was a significant relationship between the number of chronic lesions and CHA2DS2-VASc score with an average of 4.9 (95% confidence interval [CI], 2.5–7.2) additional lesions for each point increase in the CHA2DS2-VASc score (R²=0.23; P<0.0001). Patients with PELs did not have any neurological differences with a mean preablation NIH Stroke Scale score of 0.1±0.4 compared with 0.3±0.8 in patients without PEL (P=0.23; Figure 4).

Procedural Parameters

Compliance with the ablation protocol was high (Table 2). The average INR on the day of procedure was 2.4±0.5. The ACT just before initiation of ablation was 368±192 seconds and the mean procedural ACT was 405±116 seconds. All ablation catheters were introduced using the submerged technique for all procedures. Virtually all RF applications (99.8%) had either the distal or proximal electrode disabled on the circular MER catheter. Most subjects experienced a spontaneous or direct current cardioversion during the procedure (67%), with an average of 2.3±1.8 cardioversions per converted subject (55% of cardioversions were performed in the frontal lobe).
spontaneous; 45% were electrical). Total procedure time was 100±35 minutes with a LA time of 64±27 minutes. PV isolation was achieved in all subjects using only the circular MER catheter. At the 1-month follow-up visit, 53/60 subjects (88%) were in sinus rhythm (94% on antiarrhythmic drug therapy).

Incidence of ACE and Neurological Findings Postablation

The mean time elapsed after the ablation procedure until the postprocedural cerebral MRI was 28.2±16.3 hours. On the postablation MRI, 1 of 60 subjects (1.7%; 95% CI, 0.04–8.9) had any new ACE lesion seen. In this patient, there was only 1 new ACE lesion measuring 8×6 mm in the occipital lobe white matter (Figure 5). This lesion was no longer visible on the 1-month follow-up MRI. This patient was a 58-year-old woman with a history of persistent AF. Her CHADS2 score was 0 and CHA2DS2-V ASc score was 1, and she had no PEL on preablation MRI. The patient had an INR of 2.0 on the day of ablation. During the procedure, the patient experienced an elevated procedural ACT of >900 seconds after the transseptal puncture for which intravenous protamine was administered. No cardioversions were performed during the ablation. Gross neurological assessment postablation in this patient was unremarkable with a MMSE score of 29.0 and a NIH Stroke Scale score of 0.0 (baseline 30.0 and 0.0, respectively). At 1 month, the MMSE was 30.0 and the NIH Stroke Scale was still 0.0.

In the total study population, there were no significant differences in the MMSE or NIH Stroke Scale scores between baseline, postprocedure, and at 1 month (Figure 4).

Adverse Events

No subjects experienced a symptomatic cerebral event. One subject experienced 2 right groin pseudoaneurysms that resolved upon localized thrombin injection 1 day after the procedure. No other serious adverse events were noted, including pericardial effusion or tamponade, atrial esophageal fistula, or death.

Table 2. Procedural Parameters

<table>
<thead>
<tr>
<th>Procedural Parameters</th>
<th>N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR; % subjects &gt;2.0</td>
<td>2.4±0.5; 88%</td>
</tr>
<tr>
<td>Mean ACT, s</td>
<td>405±116</td>
</tr>
<tr>
<td>Minimum ACT, s; ACT before first ablation, s</td>
<td>319±130; 368±192</td>
</tr>
<tr>
<td>No. of RF applications per subject</td>
<td>28.8±16.1</td>
</tr>
<tr>
<td>No. of RF applications with E1 or E10 disabled</td>
<td>99.8±0.7%</td>
</tr>
<tr>
<td>Cardioversion, % of patients*</td>
<td>67%</td>
</tr>
<tr>
<td>No. of cardioversions (mean per patient); spontaneous</td>
<td>2.3±1.8; 55%; 45%</td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>100±35</td>
</tr>
<tr>
<td>Left atrial time, min</td>
<td>64±27</td>
</tr>
<tr>
<td>Time elapsed from end of procedure until MRI, h</td>
<td>28.2±16.3; median 22.1</td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time; E1, distal electrode on the circular multielectrode radiofrequency (MER) catheter; E10, proximal electrode on the circular MER catheter; INR, international normalized ratio; and RF, radiofrequency.

*Spontaneous or direct current cardioversion to sinus rhythm.

Figure 5. New asymptomatic cerebral embolus (ACE) lesion found in the 1 patient experiencing postablation ACE in this study. ACE was defined by an abnormality on T2–fluid-attenuated inversion recovery (FLAIR) images corresponding to restricted diffusion on the diffusion-weighted (DW) sequences. The top panels are DW MRI images and the bottom panels are FLAIR images. Images of immediate postablation (left) and 1-month postablation (right) are shown. A, A restricted diffusion defect (circled) correlates to a FLAIR abnormality in B (circled). At 1 month, however, this lesion is no longer visible (C and D).
(char) because of denaturation of tissue; and (3) thromboemboli because of activation of the coagulation cascade. In animal studies with the circular MER catheter, it was found that the largest source of gaseous and solid emboli occurred when the distal and proximal electrodes of the catheter were in close proximity or overlapping.\textsuperscript{10} This electrode overlap creates a bipolar short circuit resulting in excessive tissue and blood heating. By deactivating either the proximal or distal electrode in the current study, this important potential source of emboli was prevented.

The second largest source of gaseous emboli in the animal model was found to be introduction of air into the LA via the sheaths during catheter insertion and removal. By immersing the circular MER catheter in saline during introducer capture and by aspirating and flushing the sheath side arm, air embolism was also reduced in this study.

Finally, aggressive anticoagulation in this study mitigated any thromboembolic mechanism of ACE. Therapeutic oral VKA anticoagulation for $\geq 1$ month before the ablation and continued uninterrupted periablation likely further reduced the chance of periprocedural thromboembolic complications.\textsuperscript{8} Finally, use of a higher minimum procedural ACT of 350 seconds may also have further reduced embolic risk.\textsuperscript{14} It is interesting that the only patient with an ACE lesion postablation also had a substantial dose of intraprocedural protamine. It is unclear if protamine contributed to the ACE lesion, especially because postprocedural protamine was used in 25/60 patients (42\%) without ACE occurrence.

**Incidence and Predictors of ACE**

Prior studies have reported rates of ACE postablation ranging from 1.9\% to 14.3\% using traditional irrigated RF energy or cryoablation.\textsuperscript{3,6,7,15–20} Two studies also suggested that the rate of ACE associated with MER circular catheters was significantly higher than the ACE rate associated with irrigated RF catheters.\textsuperscript{7,8} These 2 studies used an ACT cutoff of 300 seconds but used interrupted VKA with low-molecular-weight heparin bridging periablation. There was also no specific technique for loading/unloading the catheter and no avoidance of distal-proximal electrode interaction. Two subsequent studies then reported that through application of some procedural changes, post-MER ablation ACE rates could be reduced to the 5\%–10\% range.\textsuperscript{15,17} Wieczorek et al\textsuperscript{15} used an uninterrupted VKA periablation strategy and careful underwater loading of the catheter with careful removal, with a mean ACT of 282. Their study was able to achieve ACE rates of <10\%, suggesting the importance of VKA and sheath loading techniques. The only predictor of ongoing ACE was the interaction between the distal and proximal electrodes. Nardi et al\textsuperscript{17} stressed the importance of keeping the distal and proximal electrodes apart without some of the other Wieczorek interventions, and their rate of ACE was even lower. In the current study, the ACE rate of 1.7\% is one of the lowest ACE rates ever reported (Figure 6), and in 1 patient who had a new ACE lesion, only 1 lesion was found measuring <10 mm. This would seem to stress the importance of employing all of the risk attenuation strategies, in particular avoiding the electrode...
interaction, during MER ablation. In fact, meticulousness during anticoagulation and sheath loading may help reduce ACE events regardless of ablation technology.

Prior studies also suggested that procedural ACT\(^1\) and performing cardioversion\(^2\) during the procedure were predictors of postablation ACE. ACT was likely found to be a predictor because the target of ACT in some prior studies was only \(\approx 250\) seconds. ACT levels of \(>300\) seconds have been recommended by both studies\(^3\) and guidelines\(^4\) to better reduce thromboembolic risk, and in our study, ACT was always kept \(>350\) seconds. In this study, two thirds of patients had a mean of 2.3 cardioversions per procedure. Yet, no ACE was detected in any of the converted patients. It would appear that cardioversion is not a major contributor to ACE in the setting of this trial.

Pre-existing Chronic MRI Lesions

A surprising finding of this study was the high prevalence (60%) and number of pre-existing MRI lesions seen in patients who were otherwise at low risk of chronic thromboembolism. This is higher than, but consistent with, rates of PEL reported in other studies, which have ranged from 12.3% to 58%.\(^5,6,15-17\)

This shows that even in AF patients with low CHADS\(^2\) risk scores, silent embolic lesions are still prevalent. This high burden of embolism and chronic scar formation caused by chronic AF has been shown to correlate with development of cognitive decline.\(^21-23\) In contrast, the rate of chronic ACE lesions postablation is very low, ranging from 0% to 3.5%. Even in studies demonstrating high rates of immediate post-procedural ACE, many of these lesions become undetectable on MRI after 1 to 3 months.\(^2\) This is not surprising because the bulk of emboli causing these lesions are likely gaseous and, therefore, cause only transient interruption of blood flow.\(^24\)

Furthermore, diffusion-weighted changes on MRI represent hyperacutecerebral ischemia that does not necessarily progress to full cellular necrosis.\(^25\) In the current study, the only ACE lesion detected postablation was no longer detected after 1 month. Thus, in the context of the substantial embolic risk posed by chronic AF, the contribution of catheter ablation to chronic cerebral change is quite small. If catheter ablation can reduce AF burden, it is possible that overall embolic load could also be reduced in the long term, resulting in a clear net clinical benefit. Further clinical investigation would be required to definitively answer this question.

Study Limitations

Although this study has reported an encouragingly low rate of ACE, it is only 1 study with a small to moderate number of patients. Second, this study was a single-arm cohort study without a comparative group. Thus, the incidence of ACE using alternative ablation technologies with similar procedural adjustments cannot be known from this data. Third, several procedural interventions were implemented simultaneously in this study; so it is impossible to determine the relative contributions of each intervention on the reduction in ACE rate. Based on prior animal data, the interaction between the distal and proximal electrodes was the single largest contributor to both gaseous and particulate emboli; so it could be hypothesized that this intervention was perhaps the most important measure implemented. Fourth, the neurological assessments in this study are intended for patients with suspected or symptomatic neurological impairment (MMSE and NIH Stroke Scale). Neither of these assessments can detect very subtle neurological changes, and it is possible that with highly detailed neuropsychological testing, subtle neurological changes may have been detected. Finally, neither the long-term efficacy of the MER ablation technology nor its potential to impact on chronic embolic load due to the AF disease process was assessed in this study.

Conclusions

Applying procedural changes to MER ablation significantly reduces the ACE incidence to 1.7%, which is one of the lowest reported rates of any technology. The changes do not impact acute safety or efficacy. In contrast, the prevalence of chronic preablation cerebral lesions is high despite low thromboembolic risk.

Acknowledgments

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**CLINICAL PERSPECTIVE**

This prospective, multicenter study sought to determine the rate of asymptomatic cerebral emboli (ACE) using a circular multielectrode radiofrequency (MER) catheter when specific procedural changes were applied. Sixty patients at 7 centers were studied. All ablation procedures were performed using the MER catheter plus: continuous vitamin K antagonist use (international normalized ratio >2.0) and heparin to keep activated clotting time >350 seconds; submerged loading of the catheter before insertion into sheaths to minimize air ingress; and deactivation of either the proximal or distal electrode to avoid bipolar radiofrequency interaction. Prevalence of preablation MRI brain lesions was 60% (36/60), whereas new postprocedural ACE occurred in only 1/60 patients (incidence, 1.7%), which was no longer visible on MRI after 1 month. This is one of the lowest rates of peri-procedural ACE reported.
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Supplemental Material

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eMethods 1. Cerebral Magnetic Resonance Imaging (MRI) protocol

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2. Turbo fluid attenuated inversion recovery (FLAIR) sequences
3. T2-weighted turbo spin echo sequences
4. T21.- sequence to detect bleeding
5. T1-weighted spin echo sequences

- Diffusion gradients will be applied in three orthogonal directions during diffusion-weighted imaging.
- The imaging protocol includes a sagittal T1-weighted spin echo sequence (scout) to obtain a better definition of the anterior and posterior cerebral commissures.
- Sequences will be centered on the axis defined by a line passing between the anterior and posterior cerebral commissures. The definition of this line is important to allow reproducibility of the MRI sequences before and after the procedure.
- Scans should target a slice thickness of 5mm (3mm for FLAIR and DWI). Slice thickness should not be larger than 5mm and slice gap no larger than 20%. FLAIR and DWI slice thickness should always be the same.
- All MR images are analyzed independently by 2 certified radiologists blinded to the clinical status and identity of the patients. For each patient the Lesion Log will be completed.
- On the post ablation MRI:
  1. For the purpose of the primary objective of the study following definition for determination of acute embolic lesions will be used (refs 2-5):

     An acute embolic lesion is defined as a focal hyperintense area detected by the FLAIR sequence, corresponding to a restricted diffusion signal in the DW sequence, confirmed by apparent diffusion coefficient mapping to rule out a shine-through artifact. The size and localization of the focal lesions will be analyzed.

  2. Additionally, the number of new lesions will also be determined using the definition of in accordance with the guidelines on imaging recommendations for acute ischemic stroke published by the AHA in Stroke 2009 (ref 6):

     An acute embolic lesion will be defined as focal diffusion abnormalities seen as focal, bright hyper-intensity in a cortical or subcortical location, or in the vascular territory of the perforating arteries. In addition, apparent diffusion coefficient (ADC) maps will be calculated based on the diffusion-weighted data in conjunction with the isotropic diffusion-weighted images. These will be used during image interpretation to rule out “shine through artifacts”.
• The size and localization of the focal lesions will be analyzed by the core lab.

• Follow-up examination are triggered by the detection of new intracranial lesions in the DWI1000 sequence and corresponding finding in the ADC-map following the imaging recommendation for acute ischemic stroke published by the AHA (ref 6).

**MR Hardware**

• All MR examinations should be carried out using a 1.5 Tesla MR unit employing the circular polarized head coil.

• All participating centers need to indicate the MR unit being used throughout the study.

• All study patients need to be examined with the same MR unit.

**Test MRI**

Prior to study participation, a test MRI will be send to the core lab for qualification purposes.

**Time frame for MR imaging**

MRI of the brain will be performed within 7 days before the procedure and repeated the day after the procedure to compare pre-ablation DWI (diffusion weighted images) with post ablation DW I to identify new procedure-related ischemic cerebral lesions. For patients that are positive for lesions after the procedure, a follow-up MR scan will be performed 30 days post procedure.

All imaging should be performed employing the same imaging protocol (especially imaging parameters, slice thickness as well as slice positioning) as during base line examination.

**Post processing**

DW I: ADC mapping must be provided at b=0, b= 500, and b= 1000

**Data delivery**

The complete MR data set (including all post processing images and DWI information) must be provided on CD-ROM in DICOM format together with a DICOM reader to:
Genae Associates NV
Attn. An Goethals
Justitiestraat 6b
2018 Antwerp, Belgium

The data set should include the following information:
• Study Title
• Site ID
• Patient Study ID
• Study Phase (Pre Ablation – Post Ablation – Follow up – Unscheduled)
• Days to Index Procedure (Pre / Post Ablation)
Timing Post Ablation:

The post ablation MRI has to be performed preferably the day after the ablation procedure, at least 12 hour after intervention but not later than 72h.

Sequence

Concerning the consistence of the diffusion imaging sequence it is important, that following criteria are fulfilled:

- Diffusion weighting is switched along all three directions to allow for averaging along the three spatial directions (otherwise diffusion effects can only be detected along one spatial direction).
- The echo time TE should be 88 ms (+/- 4 ms), because this is the shortest available time on the Siemens Sonata scanner (this is a critical parameter because the degree of distortions is related to it), if the number of slices is set to N = 50 (slice thickness 5 mm, gap 0, b = 0.500,1000 s/mm², bandwidth/pixel = 1302 Hz, matrix 128x96 (Partial Fourier 6/8), interpolation to matrix 256x256 (not necessary), TR = 8100ms (> 5000 ms), FOV = 230mm, 3 averages, acq.time 2:58min, interleaved).
- The slice orientation should be along the AC-PC-line (or transversal / isocentre in case of the calibration measurement). The other imaging sequences should be aligned according to the DWI sequence (copy slice angulation).
- The temperature within the scanner room has to be documented.

References

6. Richard E. Latchaw, MD, Chair; Mark J. Alberts, MD, FAHA; Michael H. Lev, MD, FAHA; John J. Connors, MD; Robert E. Harbaugh, MD, FAHA; Randall T. Higashida, MD, FAHA; Robert Hobson, MD, FAHA†; Chelsea S. Kidwell, MD, FAHA; Walter J.
Koroshetz, MD; Vincent Mathews, MD; Pablo Villablanca, MD; Steven Warach, MD, PhD; Beverly Walters, MD; on behalf of the American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, and the Interdisciplinary Council on Peripheral Vascular Disease, Recommendations for Imaging of Acute Ischemic Stroke. A Scientific Statement From the American Heart Association, Stroke, September 24, 2009; 40: 3646-3678.

Abbreviations

- ADC : Apparent Diffuse Coefficient
- DW : Diffusion Weighted
- DWI : Diffusion Weighted Images
- FLAIR : Fluid attenuated inversion recovery
- MRI : Magnetic Resonance Imaging
- MW : Molecular Weight
- PVAC : Pulmonary Vein Ablation Catheter
- RF : Radio Frequency
**ERACE Recommended MR sequences:**

TR/TE values may differ depending on MR unit used.

Utilize identical imaging protocols, slice orientation and positioning (and same MR unit), at baseline, post procedure, and follow-up imaging.

<table>
<thead>
<tr>
<th>Name</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>TI (ms)</th>
<th>Flip (°)</th>
<th>Slices (n)</th>
<th>Thick.(mm)</th>
<th>Acq.(n)</th>
<th>Dist. Fac.(%)</th>
<th>FOV(mm)</th>
<th>Orient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scout</td>
<td>20</td>
<td>5</td>
<td>40</td>
<td>1 in each orientation</td>
<td>10</td>
<td>1</td>
<td></td>
<td>20</td>
<td>280</td>
<td>sagittal</td>
</tr>
<tr>
<td>FLAIR</td>
<td>9000</td>
<td>75</td>
<td>2500</td>
<td>150</td>
<td>22</td>
<td>3</td>
<td>2</td>
<td>20</td>
<td>230</td>
<td>AC-PC</td>
</tr>
<tr>
<td>PD-T2-TSE</td>
<td>3590</td>
<td>13/94</td>
<td>150</td>
<td>24</td>
<td>5</td>
<td>1</td>
<td></td>
<td>20</td>
<td>230</td>
<td>AC-PC</td>
</tr>
<tr>
<td>T21.-</td>
<td>800</td>
<td>26</td>
<td>20</td>
<td>24</td>
<td>5</td>
<td>2</td>
<td></td>
<td>20</td>
<td>230</td>
<td>coronal</td>
</tr>
<tr>
<td>T1-SE</td>
<td>500</td>
<td>17</td>
<td></td>
<td>24</td>
<td>5</td>
<td>1</td>
<td></td>
<td>20</td>
<td>230</td>
<td>AC-PC</td>
</tr>
<tr>
<td>DW I</td>
<td>8100</td>
<td>88</td>
<td>90</td>
<td>50</td>
<td>3</td>
<td>3</td>
<td></td>
<td>0</td>
<td>230</td>
<td>AC-PC</td>
</tr>
</tbody>
</table>
eMethods 2: Descriptions of Neurological Testing Protocols

Mini Mental State Exam (MMSE):

The MMSE is a brief, 30 point questionnaire used to screen patients for cognitive impairment. A higher score is “better” with a score of 25 or more indicating near normal or normal cognition. Scores less than this can indicate severe (<10), moderate (10-20), and mild (21-24) cognitive impairment. The table below lists the categories of testing as well as samples of the questions and/or tasks requested of the patient.

<table>
<thead>
<tr>
<th>Category</th>
<th>Points</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation to Time</td>
<td>5</td>
<td>The patient is asked to list the time starting with year and then season, month, today’s date, and day of the week.</td>
</tr>
<tr>
<td>Orientation to Place</td>
<td>5</td>
<td>The patient is asked to list the place starting with country and then state, city, name of hospital, floor in hospital</td>
</tr>
<tr>
<td>Registration</td>
<td>3</td>
<td>The patient is asked to repeat the names of three objects and remember them.</td>
</tr>
<tr>
<td>Attention and Calculation</td>
<td>5</td>
<td>The patient is asked to count down from 100 by intervals of 7.</td>
</tr>
<tr>
<td>Recall</td>
<td>3</td>
<td>The patient is asked to repeat the three objects from “registration.”</td>
</tr>
<tr>
<td>Language</td>
<td>2</td>
<td>The patient is asked to name two objects when the examiner points at them.</td>
</tr>
<tr>
<td>Repetition</td>
<td>1</td>
<td>The patient is asked to repeat a phrase spoken by the examiner.</td>
</tr>
<tr>
<td>Complex Commands</td>
<td>6</td>
<td>The patient is asked to read a sentence and do what it says; write any sentence; copy a design; and execute a three stage command.</td>
</tr>
</tbody>
</table>

National Institutes of Health Stroke Scale (NIHSS):

The NIHSS is a systematic assessment tool that provides a quantitative measure of neurological deficits related to a stroke. The test consists of 11 items of assessment. Each item is graded on a three to five point scale where “0” represents normal and higher scores indicate higher levels of neurological impairment. The maximum obtainable score is 42. Total scores reflect differing degrees of neurological impairment: 0 = no stroke symptoms, 1-4 =
minor stroke, 5-15 = moderate stroke, 16-20 = moderate-severe stroke, 21-42 = severe stroke. The 11 items for assessment are listed in the table below:

<table>
<thead>
<tr>
<th>Item</th>
<th>Scored from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Consciousness</td>
<td>0-3</td>
</tr>
<tr>
<td>Level of Consciousness Questions (patient asked the month and their age)</td>
<td>0-2</td>
</tr>
<tr>
<td>Level of Consciousness Commands (asked to open/close hand, grip)</td>
<td>0-2</td>
</tr>
<tr>
<td>Best Gaze (testing of horizontal eye movements)</td>
<td>0-2</td>
</tr>
<tr>
<td>Visual Fields (upper and lower quadrants of vision tested)</td>
<td>0-3</td>
</tr>
<tr>
<td>Facial Palsy (patient asked to smile, grimace, close eyes)</td>
<td>0-3</td>
</tr>
<tr>
<td>Motor Arm (arm extended, look for drift in arm)</td>
<td>Left arm – 0-4, Right arm – 0-4</td>
</tr>
<tr>
<td>Motor Leg (leg extended, look for drift in leg)</td>
<td>Left leg – 0-4, Right leg – 0-4</td>
</tr>
<tr>
<td>Limb Ataxia (finger to nose and heel to shin testing on both sides)</td>
<td>0-2</td>
</tr>
<tr>
<td>Sensory (reaction to pinprick)</td>
<td>0-2</td>
</tr>
<tr>
<td>Best Language (describe what is happening in a picture, name items, read sentences)</td>
<td>0-3</td>
</tr>
<tr>
<td>Dysarthria (patient asked to read items)</td>
<td>0-2</td>
</tr>
<tr>
<td>Extinction and Inattention (examining if the patient is neglecting one side of body)</td>
<td>0-2</td>
</tr>
</tbody>
</table>