THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Evaluation of learning curve and safety aspects of phased radiofrequency ablation procedures for pulmonary vein isolation in atrial fibrillation

Dr. Mihran Martirosyan MD

Supervisor: Prof. Dr. Zoltán Csanádi MD, PhD, DSc

University of Debrecen

Kálmán Laki Doctoral School

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Summary

This work studied different aspects of phased radiofrequency ablation based on data from a total of 159 patients who underwent the procedure for paroxysmal or persistent atrial fibrillation. We demonstrated that the procedure is safe with no significant learning curve effect only on fluoroscopy times, but not on complication rates, procedure time and acute isolation rate of the pulmonary veins. In a subset of 27 patients the rate of silent cerebral ischemia (SCI) was assessed by comparing the results of diffusion-weighted magnetic resonance imaging of the brain before and after the ablation and correlated with the number of microemboli recorded during different stages of the procedures using transcranial Doppler. New SCI on DW-MRI after PVI was demonstrated in 6 patients (22%) with a tendency to disappear by the 3-month follow-up control with the exception of one patient who still had a detectable lesion significantly reduced in size. No significant difference in the total number of microemboli was detected in those patients who demonstrated a new acute MRI lesion versus in those who had no new lesion. However, the number of microemboli recorded during PV angiography was significantly higher in the patients with versus in those without new brain lesions. Further, multivariate logistic regression results demonstrated that the total MES count detected during the entire procedure was predictive of silent cerebral lesions at an advanced age: patients aged 68 years or older were significantly more likely, to have new brain lesions if the number of MESs was high.

Keywords: atrial fibrillation, phased radiofrequency ablation, transcranial Doppler recording, diffusion-weighted magnetic resonance imaging

2. Abbreviations

AF – atrial fibrillation

ACT – activated clotting time

AAD – antiarrhythmic drug

CA – catheter ablation

CB – cryoballoon

CI – confidence interval

DM – diabetes mellitus

DTI – diffusion tensor imaging

DW MRI – diffusion-weighted magnetic resonance imaging

DWI – diffusion-weighted image sequence

FLAIR – fluid-attenuated inversion recovery sequence

INR – international normalized ratio

iv – intravenous

LA – left atria

LV – left ventricle

LVEF – left ventricular ejection fraction

MCA – middle cerebral artery

MES – microembolic signal

MRI – magnetic resonance imaging

OR – odds ratio

PV – pulmonary vein

PVAC – pulmonary vein ablation catheter

PVI – pulmonary vein isolation

RF – radiofrequency

SCI – silent cerebral ischemia

SR – sinus rhythm

TCD – transcranial doppler

TIA – transient ischemic attack

VKA – vitamin K antagonist

3. Introduction

3.1. Treatment strategies of atrial fibrillation and influence of learning curve on outcome of pulmonary vein isolation

Catheter ablation (CA) for atrial fibrillation (AF) has emerged as an alternative to anti-arrhythmic drug (AAD) therapy after the failure of at least one AAD, or even as the first line of treatment in selected patients (1-3). Although a wide variety of ablation techniques have been used to treat AF, it is generally agreed that the cornerstone of any transcatheter procedure is the electrical isolation of all pulmonary veins (PVs). This is currently most commonly achieved by encircling the PVs with focal radiofrequency (RF) lesions under the guidance of a 3-dimensional electroanatomical mapping or navigation system. This point-by point ablation technique requires extensive operator experience for efficiency and safety, and is usually associated with long procedure times. Novel methods aiming at simpler and faster PV isolation (PVI) have therefore been developed in recent years, including cryoballoon (CB) ablation (4, 5) and multipolar RF ablation with the circular PV ablation catheter (PVAC) (6-9). These single-shot techniques were designed to create a circular ablation lesion around the PVs after the appropriate positioning of the ablation catheter at the ostium or at the antra of each PV. A number of studies have demonstrated comparable levels of success and safety profile, but shorter procedure times with these simplified methods than with the conventional point-by- point ablation (10-13).

With the continuous increase in the number of AF ablation worldwide, the procedure is being introduced into new and less experienced centers. Efficacy and periprocedural complications are known to improve with experience in any invasive procedure including AF ablation although the learning curve effect has not been extensively evaluated. Sairaku et al. have reported a significantly higher incidence of procedure-related complications and a lower arrhythmia-free survival at 6 months follow-up with the double Lasso catheter-guided encircling pulmonary vein isolation in the first as compared with the following 156 patients who underwent the ablation (14). Wojcik et al have demonstrated a learning curve effect with CB ablation as indicated by the decline in procedure and fluoroscopy times (15).

However, no studies have been performed on the learning curve of the single-shot techniques as assessed by procedural parameters and long-term efficacy.

3.2. Risk of microembolization during catheter ablation of atrial fibrillation

Clinically manifest stroke is one of the most feared complication of left atrial ablation for AF. In experienced centers the rate of this complication is below 1% in these days. However, silent cerebral ischemia (SCI) observed on diffusion-weighted magnetic resonance imaging (DW MRI) as a complication of AF ablation has been reported at much higher rates (16-22) and generated significant concern regarding the long-term consequences of these procedures. The diagnosis of SCI is based on the comparison of two cerebral DWI MR examinations, usually performed 48-72 hours apart with the AF ablation procedure carried out between them. This imaging modality provides no intra-procedural data which would suggest the mechanism of lesion formation. In contrast, bilateral insonation of the middle cerebral artery (MCA) using transcranial doppler (TCD) offers a real-time assessment of microembolization throughout the whole procedure. The use of TCD during AF ablation was first reported by Kilicaslan (23), who found a significant relationship between the number of microembolic signals (MESs) on TCD and clinical stroke events. Our group has demonstrated that the majority of MESs are gaseous and the generation of microemboli is concentrated in the phase of energy delivery with some ablation techniques (24-25). Further, the site of ablation, the ongoing rhythm and certain biophysical parameters during phased RF ablation have been found to be predictive of the rate of microembolization (26-27). No data are available on the relationship between microembolization as measured with TCD during the ablation procedure and silent cerebral ischemia as detected as a new ischemic lesion on DW MRI post-ablation.

3.3. Aim of our studies:

1. To investigate the time-dependent changes in procedure time and complication rates as a function of operator experience with PVI using phased RF and the PVAC.
2. To study the learning curve of phased RF ablation on clinical efficacy as assessed by the 1-year clinical outcome during initial experience with phased RF ablation.

3. To investigate the rate of microembolization during PVI and the incidence of new post-ablation cerebral lesions on DW MRI in patients undergoing PVI with phased RF and the PVAC.
4. To elucidate the potential relationship between the numbers of microemboli recorded during the different phases of the left atrial ablation procedure with the PVAC and post-ablation SCI.

4. Methods

The study was approved by the local ethics committee. All patients provided their signed written informed consent prior to inclusion.

4.1. Patient selection for learning curve effect study

The study included consecutive patients who underwent PVI with phased RF ablation for paroxysmal or persistent AF at our center between November 01, 2009 and April 30, 2012 and who had regular follow-up during the first 12 months post-ablation. Exclusion criteria included previous AF ablation, long-standing persistent AF, hyper- and hypothyroidism, significant valvular heart disease, heart failure of NYHA class III or IV, a left ventricular (LV) ejection fraction ≤ 40%, a left atrial (LA) diameter exceeding 50 mm, a LA thrombus, unstable angina or myocardial infarction within the last 3 months, severe chronic obstructive pulmonary disease, known bleeding disorders, contraindication to oral anticoagulation and pregnancy. All participating patients signed the informed consent form prior to the procedure.

4.2. Patient selection for microembolization and silent cerebral ischemia study

Consecutive patients undergoing PVI with the PVAC and the GENius TM 14.4 RF generator for symptomatic paroxysmal or persistent AF not adequately controlled by at least one anti-arrhythmic drug were considered for enrollment in the study. The same exclusion criteria were applied as for the learning curve effect study. All participating patients signed the informed consent form prior to the procedure. In addition, all of them were asked to consent to continuous, bilateral TCD detection during the ablation procedure, and to DW MRI examinations before and after PVI. Exclusion criteria including hyper- or hypothyroidism, heart failure, LA diameter exceeding 50 mm and previous clinical ischemic stroke or transient is-chemic attack (TIA) were applied. The study design conformed with the guiding principles of the Declaration of Helsinki, and was approved by the Institutional Ethics Committee.

4.3. Patient preparation and preprocedural evaluation

Patients were admitted to the hospital 1 or 2 days prior to the procedure. Those on oral anticoagulation with a vitamin K antagonist (VKA) continued to take the drug and the procedure was performed with an international normalized ratio (INR) in the therapeutic range. For those patients, who were not on VKA on admission to the hospital low molecular weight heparin was started twice daily in a weight-adjusted dose and administered until 12 hours prior to the procedure. All patients in the microembolization and SCI evaluation study were on uninterrupted VKA treatment with INR between 2.0 and 3.0 on the morning of the procedure. All patients were examined by transesophageal echocardiography within 24 hours prior to ablation to rule out an intracardiac thrombus.

4.4. Ablation procedure with phased radiofrequency and the multielectrode pulmonary vein ablation catheter

Ablation procedures were performed under conscious sedation with midazolam and fentanyl. Decapolar (BARD Electrophysiology Inc., Lowell, MA, USA) and quadripolar (Woxx 4 J, 6F, Biotronik, SE & Co. KG, Berlin, Germany) catheters were advanced from the femoral vein and positioned into the coronary sinus and the right ventricle. Surface electrocardiograms and bipolar intracardiac electrograms were registered with a Prucka, GE Medical digital recording system. A single transseptal puncture was performed under fluoroscopic guidance, by a standard technique using a Swartz SL (St. Jude Medical, Minnetonka, Mn, USA) transseptal sheath. This sheath was then exchanged for a deflectable 12 Fr inner lumen CryoCath sheath (Medtronic CryoCath LP, Kirkland, Quebec, Canada) to be used for guiding in left atrium under continuous flush with heparinized saline. Immediately after the transseptal puncture, a 150 IU/kg body weight intravenous (iv) heparin bolus was administered, followed by a continuous infusion to maintain a minimum ACT target level of >300 s. during ablations. In the microembolization and SCI study a minimum ACT target of 350 s. was applied. Additional iv boluses of 2000-5000 IU heparin were administered as needed to attain the minimum target ACT level. This heparinization scheme was the same regardless the ongoing rhythm (sinus rhythm versus AF) during ablation. All PVs were cannulated with a guidewire and the PVAC aiming at full electrical isolation which was confirmed based on the signals recorded from the ostia of the PVs via the PVAC electrodes as described below. Heparin was discontinued at the

end of the procedure with no protamine sulphate administered and the venous sheaths were removed 4-6 hours later or after a drop in the ACT level below 150 sec. No electrical cardioversion had been performed during the procedure or in the early post-ablation period before repeat cerebral MRI was completed in patients participating in the SCI evaluation study.

4.5. Phased radiofrequency ablation system and the multielectrode pulmonary vein ablation catheter

The circular multipolar PVAC was designed to create ostial or antral lesions of the PVs and provide distal mapping and pacing to assess PVI. The version used in our studies consisted of a 25-mm helical electrode array with 10 platinum electrodes (3-mm electrode, 3-mm spacing, 25-mm diameter), and over-the-wire tracking for enhanced PV targeting and placement stability. The distal, circular segment of the catheter was perpendicular to the catheter shaft. Thermocouples were placed as close as possible to the tissue interface for more accurate temperature monitoring (Figure 1). The ablation catheter was advanced to the left atrium through the FlexCath sheath and deployed in the antrum of each PV. The electrical conduction properties of the PV were assessed on the basis of the signals recorded by the PVAC electrodes after placement inside the ostium. Before the first RF delivery, the positions of the electrodes relative to the PV ostium were always confirmed by means of a hand-held injection (8-10 ml) of contrast medium (Optiray, Covidien Deutschland GmbH, Germany) diluted with saline in a 1:1 ratio through the FlexCath sheath, which was positioned close to the anticipated PV ostium. The saline infusion used for continuous flushing of the FlexCath sheath was interrupted for PV angiography and meticulous care was taken to eliminate any air bubbles in the sheath and in the syringe before contrast injections.

The PVAC was connected to the GENius™ Multi-Channel RF Ablation Generator which contains 12 independently controlled RF generators for each electrode in the catheter (28). A unique feature of the system is the duty-cycled phased RF energy, which is used for lesion formation via the PVAC. It monitors the temperature on each electrode and adapts the power to achieve and maintain the target temperature (nominally 60 °C). Power regulation is achieved through duty-cycling of the RF energy, rather than voltage control (Figure 2). The time-period with no RF delivery, allows accurate temperature monitoring and provides time

for the electrode to cool between RF bursts. The multi-electrode catheter design and the generator facilitate simultaneous bipolar (between the electrodes) and unipolar (from the electrode to the ground pad) delivery of energy (Figure 3). Unipolar RF delivery results in deeper lesions, while bipolar application facilitates lesions between electrodes. The generator allows the operator to select between different ratios of simultaneous unipolar and bipolar energy delivery including unipolar only, 1:1, 2:1, 4:1, or bipolar only. For example, the 4:1 energy mode indicates that 80% of the energy delivered is bipolar and the remaining 20% is unipolar. The results of bench tests indicated that the depth of the lesions was proportional to the energy mode selected, with unipolar delivery causing the deepest lesions, followed by 1:1, 2:1, 4:1 and bipolar RF application, the latter causing the shallowest lesions. The GENius™ monitors the power and the temperature on each electrode and displays to the operator when the power and temperature are sufficient to create a good lesion (bars are in green color).

RF energy was applied outside the vein in the antral region, targeting potentials of high amplitude on as many electrodes as possible for each application. Common ostia were isolated by inserting the guide wire into the different side branches and ablating subsequent segments of the targeted veins. For the initial applications, bipolar/unipolar RF delivery was usually started at a ratio of 4:1 for each PV and changed to a bipolar/unipolar proportion of 2:1 for a deeper lesion when a sufficient reduction in local electrogram amplitude could not be achieved after multiple RF deliveries. RF energy was applied for 60 s., usually 3-4 times per PV, until PVI was achieved. The PV conduction was reassessed after each RF application with the electrodes being advanced inside the ostium.

4.6. Procedural modifications to reduce silent cerebral ischemia

As data on the relationship of SCI and some technical details of phased RF ablation became available, important procedural modifications were recommended including the following:

1. Capturing the distal circular segment of the PVAC under saline before introduction into the sheath to eliminate any microbubbles possibly entrapped between the electrode arrays.

2. It was demonstrated in animal studies, that simultaneous delivery to poles 1 and 10 may result in a very high current density potentially leading to increased microembolus formation when these electrodes get close to each other due to a squeezed position of the circular segment of the catheter (Figure 4). Therefore, it was recommended to avoid simultaneous energization of these electrodes.

3. It was recommended to perform all phased RF procedures on uninterrupted oral anti-coagulation with a VKA with an INR value between 2-3 on the day of ablation. Further, non-fractionated iv heparin should be administered to reach an ACT target above 350 sec.

These modifications were gradually incorporated into our practice and applied in all patients who participated in the SCI evaluation study. Simultaneous RF deliveries to poles 1 and 10 were allowed only after fluoroscopic assessment of their positions when the interelectrode distance appeared at least twice the fixed distance between two other adjacent electrodes.

4.7. Transcranial doppler recording and evaluation

TCD recording was performed throughout the whole period of LA access. The transducer was held in place by a proprietary headpiece supplied with the system. The MCAs were bi-laterally insonated from transtemporal windows by using a multi-frequency doppler (Multi Dop T digital, DWL, QL software 2.8) which insonates simultaneously with frequencies of 2 and 2,5MHz. The system is capable of the automatic online identification of true MESs with a sensitivity of 100% and a specificity of 99.3% and also of discrimination between gaseous and solid emboli with a specificity of 96.5% (29, 30). TCD parameter settings as recommended by the consensus criteria (31) were kept constant during the procedures. The insonation depth was 45-55 mm, the sample volume was 8 mm, and the power was 60-100mW. MES counts were collected and evaluated separately during the different stages of the procedure as follows:

1. Transseptal puncture: the 30-sec. period after crossing the interatrial septum with the transseptal needle.

2. PV angiography: contrast injection through the FlexCath transseptal sheath. MESs were counted until they gradually decreased and disappeared after a marked burst, which usually followed the bolus within 5-10 sec.

3. Energy delivery: from the start until 15 sec. after the termination of energy delivery.

4. The remainder of the procedure: that part of the LA access period during which none of the aforementioned maneuvers were performed.

As bilateral recording was technically not possible in all patients, MES counts were calculated as mean MES count per patient, using either the mean of the bilateral counts when both sides were measured, or the unilateral data when only one side was available.

4.8. Cerebral magnetic resonance imaging

Cerebral MRI was performed the day before and within 48 hours after the procedure, using a GE Sigma Excite 1.5 T (GE Medical Systems, Milwaukee, USA) scanner and an 8-channel phased array head coil. A routine brain imaging protocol was performed, including anaxial diffusion-weighted (DWI) single-shot spin echo echo-planar sequence [diffusion gradient b-values of 0 and 1000 s/mm2, repetition time (TR): 8700ms, echo time (TE): 104ms, slice thickness: 5 mm, matrix: 128x128], an axial T2-weighted fast spin echo (TR: 5640 TE: 95ms, slice thickness: 3 mm, matrix: 320x256), a sagittal T1-weighted spin echo (TR: 480ms, TE: 12ms, slice thickness: 3 mm, matrix: 256x160) and a coronal fluid attenuated inversion recovery (FLAIR) [TR: 8002ms, TE: 130ms, slice thickness: 4 mm, matrix: 320x160] sequence. In addition, a 25 directions DTI sequence was performed for advanced diffusion mapping.

DW MRI data were analyzed by two radiology experts blinded to the clinical status of the patients. The pre-procedure MRI was compared with the post-procedure MRI to identify any new procedure-related acute cerebral lesion defined as a focal hyper-intense area detected on the DWI confirmed by apparent diffusion coefficient mapping to rule out a shine-through artifact. The size and localization of focal diffusion abnormalities were analyzed. For patients, who were positive for a new DWI lesion in the post-procedure MRI, another follow-up MRI was performed 3-month post-ablation.

4.9. End points

The acute endpoint of the procedure was the electrical isolation of all PVs, as confirmed by an entrance block evidenced by the disappearance of PV potentials in sinus rhythm (SR), during coronary sinus pacing or during atrial fibrillation.

Long-term efficacy was defined as freedom from any atrial arrhythmia without a Class I or Class III AAD after one procedure at 12 months follow-up with a blanking period in the first 3 months.

Significant peri-procedural complications were defined as any injury which resulted in death or had long-term sequel, required an immediate intervention or prolonged hospital stay.

4.10. Follow-up

Patients were usually discharged within 2 days after the ablation. Following the procedure a VKA was continued for at least 3 months. Patients taking an AAD before the procedure continued the medication for 3 months post-ablation. It was then discontinued if the patient was free of an AF relapse. VKA was discontinued 3 months after the ablation only in patients with a CHADS-VASC score of 1 or below, while those patients with a higher stroke risk were kept on oral anticoagulation regardless the results of postablation arrhythmia monitoring. Follow-up visits were scheduled at 6 weeks, and 3, 6, 9 and 12 months post-procedure.

The 12-lead ECG was checked at each follow-up. Additionally, 24-hours holter monitoring was performed at least twice, and also transtelephonic monitoring 3 times for 14- 21 days, during the first 6 months. Patients were asked to transmit their rhythm at least 2-3 times a day, and always in the event of any palpitation. During non-telemetry periods of follow-up, patients were encouraged to visit the nearest hospital or outpatient facility to document their rhythm on an ECG whenever they felt any abnormality of their heart beat. Arrhythmia recurrence was defined as any atrial arrhythmia lasting for 30 sec. or longer. The definition of long-term success was freedom from any atrial arrhythmia without any AAD, after one procedure with a blanking period in the first 3 months.

4.11. Statistical analysis

4.11.1. Statistical analysis for the learning curve study

For the learning curve effect study, the study period was divided into tierces to include the same number of patients who underwent AF ablation within each tierce. Clinical characteristics, procedural and follow-up data for subjects in each tierce were presented using numbers and frequencies (%) for categorical variables and means with standard deviations (SD) for continuous variables. Statistical calculations were performed with IBM SPSS Statistics 20 Software. The distribution was examined with Kolmogorov-Smirnov test. Discrete variables were analyzed using Chi-square test. ANOVA (Analysis of variances) and Kruskal-Wallis were used for comparisons of groups. Cox regression as univariate test was used to estimate the hazard ratio. P value less than 0.05 was considered significant.

4.11.2. Statistical analysis for the microembolization and silent cerebral ischemia evaluation study

For the microembolization and SCI evaluation study, complete data sets for all patients were collected, including the results of intra-procedural TCD monitoring, pre- and post-ablation DW MRI. Patient and procedural characteristics were evaluated by using means and standard deviation (SD) or medians and interquartile range for continuous variables accordingly, and counts and percentages for categorical variables. Groups of patients with and without DW MRI lesions were descriptively compared in terms of MES counts using Wilcoxon Rank Sum test. Logistic regression was used to evaluate the adjusted relationship between MES count and lesion development. Age was used as an a priori adjustment factor. Other potential explanatory variables were assessed for inclusion in the model. To improve distribution normality, age was cubic transformed, and the total MES count per MCA was natural log transformed. As curvature was observed in the relationship, a squared term for the log MES count was also used. Interactions were detected between the log MES count and age cubed, and between the squared log MES count and age cubed, and were therefore, included in the model. The effects of the MES count were expressed by comparing the odds for lesion development at a MES count of 1500 (a value close to the sample 75th percentile) to that at a count of 1100 (close to the sample median) in terms of odds ratios and 95% confidence

intervals, specifically for levels across the range of age within which lesion development was observed. Model checking was based on the Hosmer–Lemeshow goodness of fit test.

5. Results

5.1. Results of learning curve study

A total of 132 patients were enrolled. Pre-ablation clinical characteristics of the first, second and third 44 patients who underwent PVI with phased RF ablation are displayed in Table 1. Significant differences between the 3 tierces were found in the age and in the LA size only.

A total of 177 PVs were successfully isolated out of the 177 targeted in Tierce 1, while 173/176 and 169/171 in Tierces 2 and 3, respectively ($p>0.05$).

All PVs were successfully isolated in 44 (100%), 41 (93.8 %) and 42 (95.5 %) patients in Tierce 1, 2 and 3, respectively, ($p=0.233$). However, the number of RF applications (per PV) needed for isolation demonstrated a significant decrease with experience (6.22 SD: 2.43; 4.65 SD: 1.32 and 4.12 SD: 1.2 in Tierce 1, 2 and 3, respectively; $p<0.001$). Procedure times demonstrated a trend for lower values in Tierces 2 and 3 but the difference did not reach the level of statistical significance. In contrast, a significant decrease in fluoroscopy times was demonstrated (Figure 5).

Pericardial tamponade requiring percutaneous subxiphoid drainage occurred in the 104th consecutive patient (Tierce 3) as the only significant procedural complication.

Atrial arrhythmia-free survival rates without AAD at 12 months postablation were 68%, 75%, and 70.75% in Tierce 1, Tierce 2 and Tierce 3, respectively ($p=0.772$). On Cox proportional hazard analysis which included clinical and procedural variables no significant predictor of arrhythmia recurrence was demonstrated (Table 2).

5.2. Results of microembolization and silent cerebral ischemia study

5.2.1. Patient and procedural characteristics

A total of 36 consecutive patients who underwent PVI with the PVAC and the GENius 14.4 generator gave consent to pre- and post-ablation cerebral MRI and to intraprocedural TCD monitoring. Two patients withdrew their consents from post-ablation MRI. TCD recording of MESs with sufficient quality could not be achieved in 7, thereby the full data sets of 27 patients were available for analysis (Table 3).

A total of 108 PVs were successfully isolated. The mean (SD) procedure and fluoroscopy times were 106 (27.1) and 23 (10) minutes, respectively. Procedural complications included 1 case of pericardial tamponade which required pericardiocentesis. Clinical stroke did not occur in any of the patients during or within 1 month after the ablation.

5.2.2. Transcranial doppler and magnetic resonance imaging results

The median (interquartile range) MES count per patient was 1151 (584). The highest rate of microembolization in any stage of the procedure was recorded during RF delivery (Figure 6) and the majority of the MESs were gaseous during all phases of data collection (Figure 7).

New SCI on DW-MRI after PVI was demonstrated in 6 patients (22%): a single lesion in 2, two lesions in 3, and three lesions in 1 case (Table 4). The average (SD) lesion diameter was 7.05 (2.9) mm (4.1-13.4 mm). The majority of these lesions had disappeared by the 3-month follow-up: 1 patient had only a single lesion still detectable with a significant size reduction, and no new lesion as compared with the post-ablation image was demonstrated in any patient.

Several clinical parameters were investigated as possible predictors for SCI, including age, gender, LA diameter, LVEF%, CHA_2DS_2-VASC score, lacunary infarction on the pre-ablation MRI, the total energy delivery time, the number of contrast injections during the procedure, the percentage of concomitant use of E1/E10 and the mean intra-procedural ACT (Table 5). There was no significant difference among baseline clinical parameters between patients with and without new SCI.

5.2.3. Association between microembolization and magnetic resonance imaging lesions

Comparative analysis between TCD and MRI results is shown in Table 4. The total median MES count (interquartile range) during the procedures among the patients who demonstrated new acute MRI lesions was 1642.25 (912) as compared with 1019 (529) recorded in those who had no new lesions, the difference did not reach the level of statistical significance at this

patient cohort size (p=0.129). However, the MES count per patient recorded during PV angiography was significantly higher in the patients with versus those without new brain lesions: 257(249) vs 110 (71), respectively (p=0.0009). Further, the multivariate logistic regression results demonstrated that the total MES count detected during the entire procedure was predictive of silent cerebral lesions at an advanced age: patients aged 68 years or older were significantly more likely, in a progressive manner to acquire new brain lesions if the number of MESs was high (Table 6).

6. Discussion

6.1. Learning curve study

Main findings

This study assessed the effects of learning curve on procedural parameters and long-term success during phased RF ablation with the PVAC. Fluoroscopy time and the number of RF applications required for successful PVI declined progressively with more experience, and a similar trend was observed for procedure time. Importantly, no learning curve effect was demonstrated in the success and complication rates. However, as the potential effect of experience on these outcomes within one tierce, which consisted of 44 patients was not evaluated, this model is not suitable to make a clear distinction between no learning curve effect or a steep learning curve.

Previous studies on learning curve in atrial fibrillation ablation

Although AF ablation is considered technically more challenging compared with other ablation procedures, very limited data have been published on the significance of operator experience in relation to the safety and efficacy of the procedure. The first study that specifically addressed the importance of the learning curve during AF ablation was published by Sairaku, who reported on the results of the first 208 consecutive PVIs with point-by-point focal RF ablation in a medium-volume center (14). A significant learning curve effect has not only been demonstrated in procedure and fluoroscopy times, but also in complication rates and in the arrhythmia-free survival at 6-month follow-up. In another study summarizing the experience, on 641 AF ablations at Johns Hopkins Hospital complication rates were 9% during the first 100 and 4.3% during the subsequent 541 procedures (32). A worldwide survey (33) and the most recent consensus statement on AF ablation (1) also suggest that safety and efficacy results are better in centers performing more than 100 procedures annually. These recommendations are largely based on the experience gained with focal RF ablation.

Single-shot AF ablation techniques have been introduced to simplify and speed up PVI procedures. Available data on the influence of operator experience as related to the safety

and efficacy results with these simplified approaches are also limited. Wójcik et al. reported on the procedural experience gained over 8 years with CBA in a high-volume center (15). A continuous decrease in fluoroscopy and procedure times was observed in each subsequent year and in multivariate analysis both the year of procedure and the pre-ablation ALARMEc (Atrial fibrillation type, LA size, Renal insufficiency, MEtabolic syndrome, cardiomyopathy) risk score were independent predictors of procedure and fluoroscopy times. However, no significant decrease in complication rate over the 8-year period has been demonstrated. The overall success rate at 12 months post-ablation was 73%, which improved with each subsequent year, however this was related to the gradual fall in the ALARMEc risk score. In another single center study, the learning curves for PVI with phased RF ablation vs. with the CardioFocus laser balloon have been compared in the first 50 patients undergoing PVI with each technology (34). Procedure and fluoroscopy times decreased with time in both technologies. Atrial arrhythmia recurrence 6 months after a single procedure improved significantly from the first tierce (31.2%) to the second (17.6%) and to the third (0%) with CardioFocus laser balloon but no clear improvement was found with phased RF ablation.

These published data are in line with our results and suggest that the influence of operator experience on clinical success and procedural complications of AF ablation may be less significant with a single-shot as compared with the conventional method. This is further supported by the initial experience of a center with AF ablation (35). The first 109 patients at this center underwent PVI with either 3-dimensional guided focal RF or with phased RF ablation. The 6-month success rate was significantly higher with phased RF (68%) as compared with focal (39%) ablation, while complication rates were similar. Procedure and fluoroscopy times were also significantly shorter with phased RF ablation.

Although studies on direct comparison of PVAC with point-by-point PVI are limited, similar success rates have recently been reported with the two techniques (36). In a multicenter prospective randomized comparison, the arrhythmia-free survival at 12 months was 56% with wide-area circumferential ablation and 60% with phased RF ablation in patients with paroxysmal AF. The efficacy of PVI with the PVAC without any other LA ablation target in more chronic forms of AF is yet to be determined (37). Although the TTOP-AF study evaluated phased RF ablation in such patient cohort, other ablation catheters (multi-array ablation catheter and multi-array septal catheter) to target low amplitude high frequency complex fractionated electrograms on the LA posterior wall and septum were also used in that study.

The ongoing Victory-AF trial is currently enrolling patients with persistent and long-standing persistent AF using PVAC GOLD the new generation of the PVAC catheter (38).

Potential implications for clinical practice

Available data suggest that the learning curve in PVI and the influence of previous operator experience on relevant procedural and clinical endpoints might be ablation technology-dependent. Ablation with a single-shot device can be performed not only with shorter procedure and fluoroscopy times as compared with focal ablation, but also with more satisfactory clinical outcome by a well-trained electrophysiologist who is proficient in transseptal catheterization and LA ablation but is in the early phase of his AF ablation practice. Further, any of these simplified approaches might be a reasonable choice for lower volume centers as a regular performance of a higher number of procedures is required not only to develop but also to maintain the adequate technical skills with point-by-point ablation.

Limitations of the study

This study has several limitations. First, this was a single center, observational patient cohort study including a relatively small number of patients thereby limiting the statistical power. There was, however, no selection bias for the study as consecutive patients undergoing AF ablation with phased RF were enrolled. Second, the main operator in all procedures had gained previous, although limited experience with CBA before he started this study, which required somewhat similar skills as ablation with the PVAC, therefore these results may not necessarily apply to what could be achieved by someone with absolutely no experience in AF ablation. Third, although high incidence of new silent cerebral ischemia detected by diffusion-weighted magnetic resonance imaging was reported after phased RF ablations [39, 40], this subclinical complication was not assessed in this study. However, most recent data indicated a very substantial reduction in silent cerebral embolization thanks to some technical and procedural modifications in phased RF ablation [41, 42].

6.2. Silent cerebral ischemia evaluation study

As far as we are aware, this is the first study that has assessed the relationship between post-ablation SCI on DW MRI and the number of microemboli detected by TCD during PVI. We demonstrated a higher total MES count recorded during the overall LA access time in patients with a new lesion on DW MRI (median: 1642 vs 1019) though the difference did not reach the level of statistical significance at this limited number of patients with positive MRI findings. Nonetheless, the relationship between the total MES count and SCI among the older patients was significant, suggesting that not only the microembolic load to the brain, but also the status of the cerebral vasculature might be relevant in lesion formation. Reduction of microembolus generation to the lowest possible level therefore seems especially important in the elderly, and it should be considered as far as selection of the ablation technique is concerned in this patient cohort. Further, the additional risk of SCI has to be considered in these patients.

The MES count recorded during PV angiography proved to be a significant predictor of new cerebral lesions in our study. As the number of microemboli recorded during PV angiography comprises only a relatively small fraction of the total MES count recorded throughout the entire procedure, the strong correlation with SCI was somewhat unexpected. Although the majority are gaseous, similarly to those recorded during other phases of the procedure, the physical characteristics of MESs generated during contrast injections may differ. Moreover, PV angiography involves the injection of rapid boluses of contrast material into the systemic circulation, and the micro-emboli, although relatively small in numbers, are thereby, introduced in a very short time. It may be speculated that, besides the number of microemboli, the intensity of these microembolic showers reaching the brain circulation might also be an important determinant of lesion formation.

Our results are in line with recent data published from the Mayo Clinic. In an elegant in vivo pig model Takami et al (43) performed different catheter, sheath manipulations and ablations while measuring microembolization using ICE, Carotid Doppler, and an extracorporeal circulation loop which included a microbubble counter and blood filters to collect particles. Significant microbubble formation was demonstrated on ICE, Carotid Doppler and in the loop during PV angiography and sheath flushing at a high flow, while micro-particles were mostly found during catheter dragging and after a steam pop. Our findings in patients seem to support these experimental data and may well have important practical implications as

around half of the ablation centers worldwide (44) routinely perform PV angiography during PVI.

Importantly, our definition of SCI was any new finding concerning the DW sequence with or without FLAIR positivity. This is different from the definitions used in most other studies (16, 17, 21, 22). We chose this more sensitive criterion so as to be able to consider any detectable brain ischemia for comparison with the MES data. FLAIR positivity was found in 5 of 6 patients and in 6 of 11 lesions in our study, and the majority of the lesions had resolved by the 3-month follow-up

Although the aim of this research was to assess the relationship between TCD and DW MRI findings and not to evaluate the safety of phased RF ablation, it is noteworthy that lower incidences of SCI have been found in recent multicenter studies (45, 46). This favorable trend has been attributed to procedural modifications of phased RF ablation based on the results of clinical and preclinical studies (47, 48). RF delivery to electrodes 1 and 10 getting close to each other due to a wedge position of the PVAC loop has been identified as the most significant contributor to embolus generation due to a high current density, therefore simultaneous energization of these electrodes was prohibited in these trials and electrode 10 even been removed from the novel PVAC Gold. Concomitant RF application on poles 1 and 10 was however not a priori excluded in our study, only when the interelectrode distance on fluoroscopy was considered unsafe. Nonetheless, this more „liberal'' practice did not contribute to a higher incidence of SCI lesions in our study.

The importance of SCI after AF ablation is still unclear. The concern that these lesions might be related to a cognitive decline is supported by limited data (49, 50). It has also been suggested that these lesions might be viewed as surrogates for the clinical stroke risk and are useful for an assessment of the risk involved with different ablation techniques and procedural changes (51). Our data suggest that TCD detection during left atrial ablation might improve our understanding of the micro-embolization process during these procedures.

7. **New observations from our studies:**

1. No learning curve effect as a function of operator experience was demonstrated during PVI procedures using phased RF and the PVAC based on time dependent changes in procedure time and complication rates, the acute success and the long-term arrhythmia-free survival.
2. A learning curve effect with phased RF ablation was demonstrated only in fluoroscopy times and in the number of RF applications.
3. No significant difference in the total number of microemboli was detected in those patients who demonstrated versus in those who did not new SCI on DW-MRI post-ablation.
4. Significantly higher number of microemboli were recorded during PV angiography in those patients who demonstrated new SCI after the procedure.

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9. Scientometry

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List of publications related to the dissertation

1. Nagy-Baló, E., **Martirosyan, M.**, Sándorfi, G., Hajas, O., Lánczi, L., Berényi, E., Ladányi, L., Kiss, A., Édes, I., Csanádi, Z.: Cerebral micro-embolization during pulmonary vein isolation: relation to post-ablation silent cerebral ischemia.
   Cardiol. J. [Epub ahead of print], 2017.
   DOI: http://dx.doi.org/10.5603/CJ.a2017.0030
   IF: 1.13 (2015)
2. **Martirosyan, M.**, Kiss, A., Nagy-Baló, E., Sándorfi, G., Tint, D., Édes, I., Csanádi, Z.: Learning curve in circular multipolar phased radiofrequency ablation of atrial fibrillation.
   Cardiol. J. 22 (3), 260-266, 2015.
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Address: 1 Egyetem tér, Debrecen 4032, Hungary Postal address: Pf. 39. Debrecen 4010, Hungary
Tel.: +36 52 410 443 Fax: +36 52 512 900/63847 E-mail: publikaciok@lib.unideb.hu, ▫ Web: www.lib.unideb.hu

List of other publications

3. Kiss, A., Sándorfi, G., Nagy-Baló, E., **Martirosyan, M.**, Csanádi, Z.: Phased RF Ablation: results and Concerns.
J. Atr. Fibrillation. 8 (1), 45-53, 2015.
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03 April, 2017

Address: 1 Egyetem tér, Debrecen 4032, Hungary Postal address: Pf. 39. Debrecen 4010, Hungary
Tel.: +36 52 410 443 Fax: +36 52 512 900/63847 E-mail: publikaciok@lib.unideb.hu, ¤ Web: www.lib.unideb.hu

9. Tables and figures

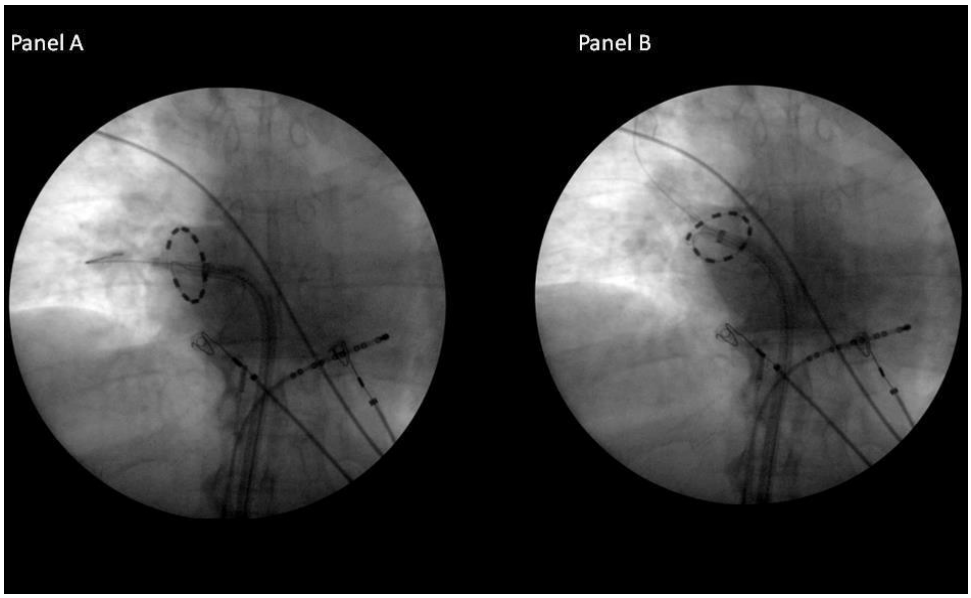

Figure 1. PVAC positioned in the right superior pulmonary vein.

Note: Electrodes 1 and 10 are widely separated on panel **A** and getting in close proximity on panel **B.**

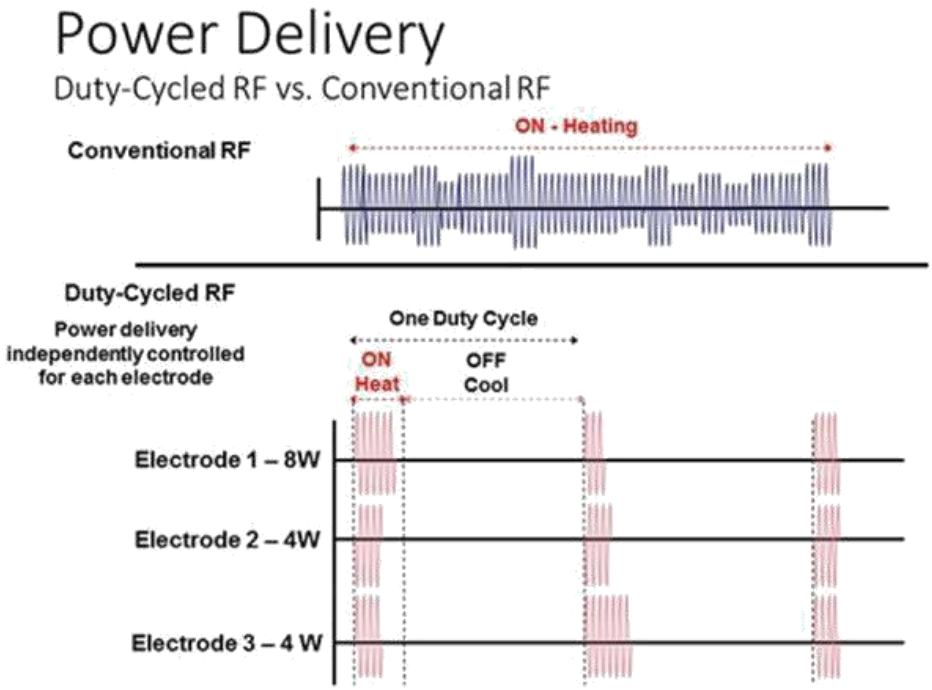

Figure 2. Duty-cycling of RF energy.

While continuous RF energy is delivered during conventional RF ablation, on and off periods alternate during duty-cycled ablation. The length of the on time is regulated to reach and maintain the target temperature. The time-period with no RF delivery allows accurate temperature monitoring and provides time for the electrode to cool between RF bursts. (Image courtesy of Medtronic Inc.).

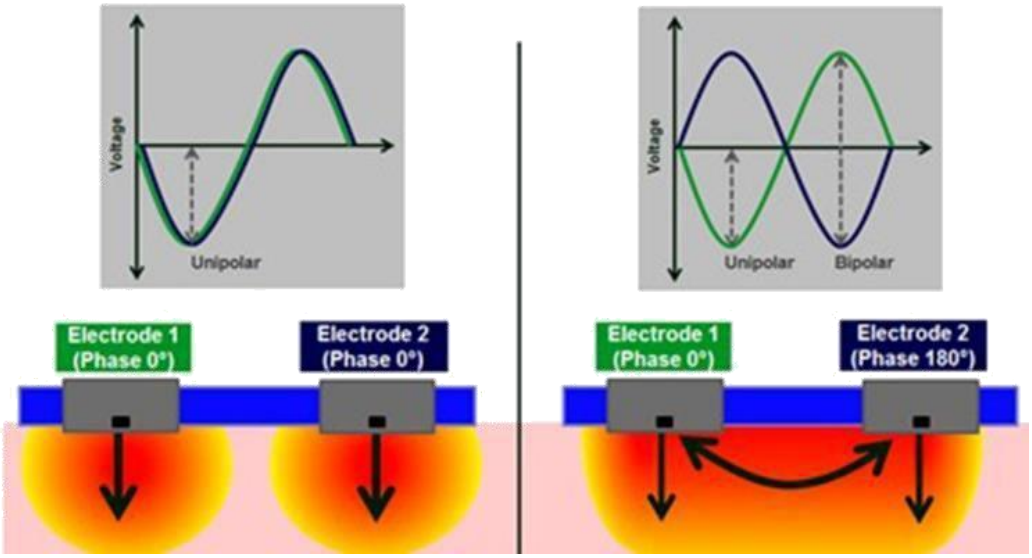

Figure 3. The concept of unipolar and bipolar energy delivery (phasing).

The multi-electrode catheter design and the generator enable simultaneous bipolar (between electrodes) as well as unipolar (from electrode to ground pad) delivery of RF energy. There is no voltage difference thus no current flow between neighboring electrodes while in phase, so only unipolar energy is delivered between each electrode and the ground pad (left). When the voltages for the two adjacent electrodes are out of phase (right), interelectrode voltage difference results in bipolar RF delivery. Different ratios of simultaneous unipolar and bipolar energy delivery including unipolar only, 1:1, 2:1, 4:1, or bipolar only can be selected. (Image courtesy of Medtronic Inc).

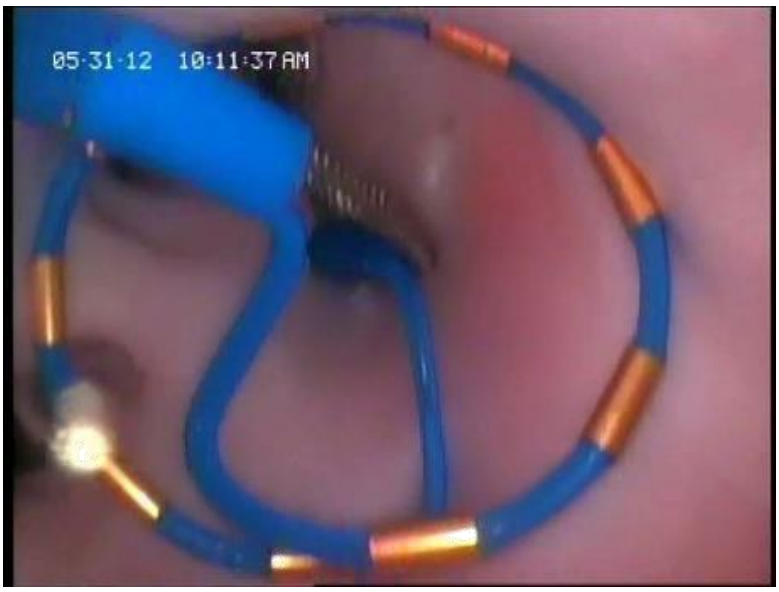

Figure 4. Electrodes 1 and 10 touching each other due to a squeezed circular segment of the catheter (intraatrial video frame from a cadaver heart, courtesy: Dr. Csanadi and Medtronic Inc).

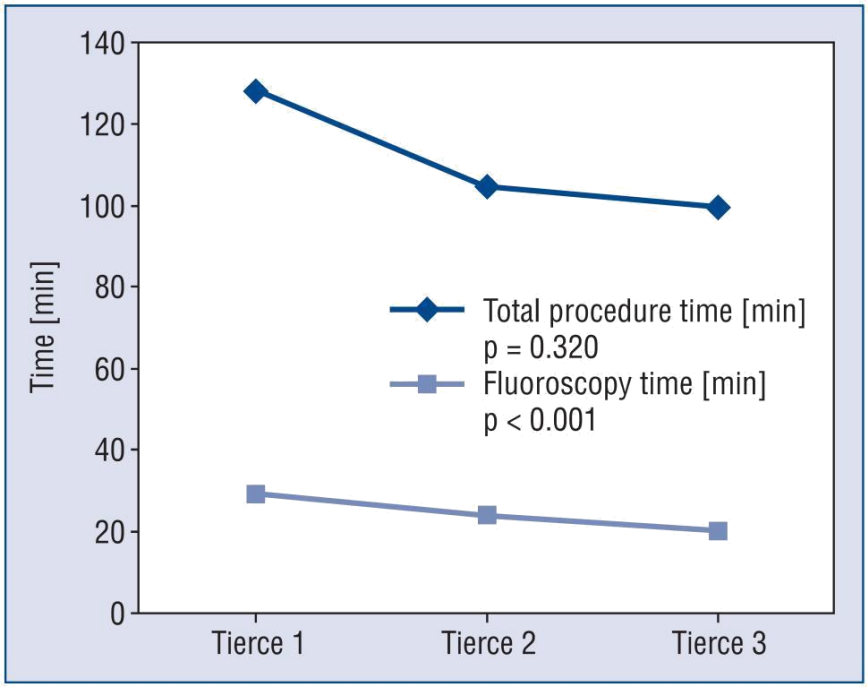

Figure 5. Procedure and fluoroscopy times in each tierce.

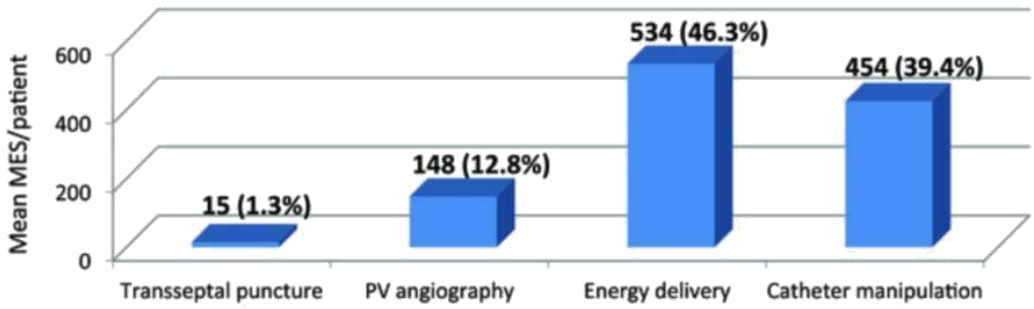

Figure 6. Total MES counts during different stages of the procedure

Figure depicting the number of MESs recorded during different stages of the PVI. The highest rate of micro embolization in any stage of the procedure was recorded during RF delivery.

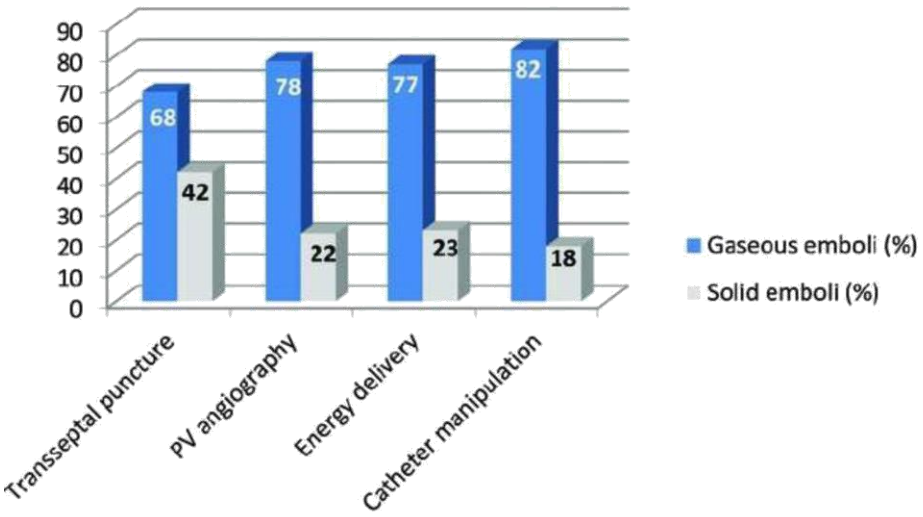

Figure 7. Ratio of solid versus gaseous emboli during different stages of the procedure

Figure illustrating the percentage of solid and gaseous micro-emboli detected during PVI. The majority of the MESs were gaseous during all phases of data collection.

Patient characteristics	Tierce 1	Tierce 2	Tierce 3	P-value
Age	55.12 ± 10.13	54.85 ± 10	59.82 ± 10.45	0.04
Male/female	33/11	31/13	28/16	0.506
Type of atrial fibrillation: Persistent	10 (22.72%)	9 (20.45%)	3 (6.82%)	0.096
Medical history:				
Hypertension	31 (70.45%)	29 (65.9%)	36 (81.8%)	0.225
Diabetes	5 (11.36%)	8 (18.18%)	7 (15.9%)	0.662
Coronary artery disease	4 (9.1%)	6 (13.63%)	9 (20.45%)	0.311
Left atrial diameter (mm)	40.61 ± 4.6	43.16 ± 4.98	42.11 ± 4.35	0.039
Left ventricular ejection fraction (%)	55.45 ± 6.1	54.52 ± 7.69	55.43 ± 7.95	0.792

Table 1. Baseline clinical characteristics in each tierce.

Variable	Hazard ration	AF free survival 95% confidence interval	P value
Gender	1.352	0.589 - 3.106	0.477
Age	1.019	0.978 - 1.061	0.376
Persistent AF	1.291	0.542 - 3.078	0.564
Hipertension	0.970	0.390 - 2.409	0.947
Coronary artery disease	1.266	0.467 - 3.437	0.643
Diabetes	0.808	0.301 - 2.165	0.671
Left atrial diameter	1.001	0.925 - 1.083	0.985
Left ventricular ejection fraction	0.988	0.940 – 1.038	0.629
Total procedure time	0.996	0.987 - 1.005	0.372
Fluoroscopy time	1.026	0.986 - 1.068	0.207
Group I			0.839
Group II	0.777	0.337 - 1.793	0.555
Group III	0.898	0.383 - 2.106	0.805

Table 2. Cox regression analysis on 12-month arrhythmia-free survival.

Parameter	N of patients
Age (years); median (interquartile range)	64 (13.23)
Male / Female	21 / 6
LA diameter (,,); mean (SD)	41.88 (4.39)
LVEF%; mean (SD)	56.77 (3.61)
CHADS2-Vasc (n)	
0	2
1	10
≥2	15
Lacunary infarction present on pre-ablation MRI; n (%)	16 (59.2)
Total energy delivery time (sec.); mean (SD)	1001.63 (280.47)
Number of contrast injections; mean (SD)	5 (3)
E1-E1- concomitantly active (% of the Eds) (SD)	34.2 (21.45)
ACT (sec.); median (interquartile range)	341 (52)

Table 3. Baseline clinical and procedural parameters of the study population (n=27).

Patient	N of lesions	Lesion size (mm)	Presence on DWI	Presence on FLAIR	Persistent lesion on 3 month control MRI
1	2	8.5	yes	yes	no
		9.5	yes	yes	no
2	1	4.6	yes	yes	no
3	3	4.4	yes	no	no
		4.9	yes	no	no
		6.6	yes	no	no
4	2	4.7	yes	no	no
		8.6	yes	yes	no
5	2	8.3	yes	yes	yes
		4.1	yes	no	no
6	1	13.4	yes	yes	no

Table 4. MRI lesion characteristics after PVI.

	Patients with DW MRI lesions	Patients without DW MRI lesions	P-value
N	6	21	
Age (years); median (interquartile range)	63.7 (12.3)	65.5 (7.1)	0.22
Male / Female	5 / 1	16/ 5	0.596
LA diameter (mm); median (interquartile range)	41 (4)	42 (6)	0.452
LVEF%; median (interquartile range)	55 (4)	57 (5)	0.2
CHA_2DS_2-Vasc; median (interquartile range)	2 (1)	2 (2)	0.513
Lacunary infarction present on pre-ablation MRI; n (%)	4 (66.67%)	13 (61.9%)	0.613
Total energy delivery time (sec.); median (interquartile range)	1045.3 (263)	978 (382)	0.64
N of contrast injections; median (interquartile range)	5.5 (5)	4 (1)	0.179
E1-E10 concomitantly active (%of the EDs); median (interquartile range)	21 (10)	36 (30)	0.121
ACT (sec.); median (interquartile range)	351.2 (58)	341 (50)	0.43

Table 5. Clinical and procedural parameters in patients with or without new silent ischemic lesions.

MES count during different stages of the procedure	Patients with DW MRI lesions	Patients without DW MRI lesions	P-value
N	6	21	
Total MES/MCA during transseptal puncture; median (interquartile range)	11.5 (11.5)	4.75 (7)	0.759
Total MES/MCA during PV angiography; median (interquartile range)	257 (249)	110 (71)	0.0009
Total MES/MCA during energy delivery; median (interquartile range)	559 (679.5)	560.5 (450.5)	0.521
Total MES/MCA during catheter manipulation; median (interquartile range)	541.25 (573)	382 (251)	0.35
Total MES/MCA during the whole procedure; median (interquartile range)	1642.25 (912)	1019 (529)	0.129

Table 6. Transcranial Doppler results in patients with or without new lesions on post-ablation DW MRI.

Age	OR	95%CI	p
54	0.15	0.02 - 1.35	0.0904
56	0.22	0.03 - 1.46	0.1175
58	0.34	0.07 - 1.62	0.1779
60	0.55	0.16 - 1.90	0.3465
62	0.92	0.34 - 2.47	0.8677
64	1.58	0.62 - 4.03	0.3389
66	2.81	0.90 - 8.79	0.0759
68	5.18	1.12 - 24.04	0.0356
70	9.92	1.29 - 76.05	0.0273
72	19.72	1.45 - 268.13	0.0251

Table 7. Logistic regression effect estimates for a contrast of 1500 vs 1100 in total MES count on the odds of MRI lesion development across the observed range of age levels

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