

Elsevier Editorial System(tm) for International Journal of Cardiology  
Manuscript Draft

Manuscript Number: IJC-D-14-00422R1

Title: Cerebral microembolization during atrial fibrillation ablation: comparison of different single-shot ablation techniques

Article Type: Original Article

Keywords: atrial fibrillation, pulmonary vein isolation, transcranial Doppler, cerebral microemboli

Corresponding Author: Dr. Alexandra Kiss,

Corresponding Author's Institution:

First Author: Alexandra Kiss

Order of Authors: Alexandra Kiss; Edina Nagy-Balo, MD; Gábor Sándorfi, MD; István Édes, MD, PhD, Dsc; Zoltán Csanádi, MD, PhD

Manuscript Region of Origin: HUNGARY

**Abstract:** Background: Clinically silent cerebral ischemia (SCI) detected by diffusion-weighted MRI has been reported in 5-40% of patients undergoing pulmonary vein isolation (PVI). Although initial reports suggested a high rate of SCI with phased radiofrequency (RF) ablation on use of the pulmonary vein ablation catheter (PVAC), the incidence was subsequently markedly reduced in consequence of procedural modifications in recent studies.

We analyzed cerebral microembolization as assessed with transcranial Doppler during phased RF ablation and with two other single-shot AF ablation technologies: the cryoballoon (CB) and the nMARQ™ multipolar irrigated RF ablation system.

**Methods and results:** A total of 89 patients (mean age: 57, SD: 12 years; 62 male) with paroxysmal or persistent AF, underwent PVI. Phased RF was used according to the initial protocol in 7 patients (PVAC Group I), with procedural modifications and a newer (14.4) version of the RF generator in 37 patients (PVAC Group II) and with the most recent (version 15.0) generator in 18 patients (PVAC Group III). Ablation was performed with the CB in 13 and with the nMARQ system in 14 patients.

The number of microemboli (mean+(SD) detected in the middle cerebral arteries was 2703(918) in PVAC Group I, 1087(542) in PVAC Group II, 719(469) in PVAC Group III, 1057(784) with CB and 2166(1047) with nMARQ ( $p < 0.01$ ).

**Conclusion:** Significant decreases in MES counts were observed thanks to the procedural modifications and newer RF generator with phased RF. High MES counts comparable to those with the initial phased RF resulted from the use of nMARQ.

Suggested Reviewers:

Ms. Ref. No.: IJC-D-14-00422

Title: Cerebral microembolization during atrial fibrillation ablation: comparison of different single-shot ablation techniques.

International Journal of Cardiology

Prof. Andrew J.S. Coats

Editor in Chief,

International Journal of Cardiology

Dear Professor Coats,

We are grateful to the Editors of *International Journal of Cardiology* and the reviewer for the evaluation of our manuscript "Cerebral microembolization during atrial fibrillation ablation: comparison of different single-shot ablation techniques. (Ref. No.: IJC-D-14-00422) as well as for the opportunity to resend its revised version. Please find our responses and the revised paper attached. We did our best to respond to all questions and concerns of the reviewer and to modify the manuscript according to her/his suggestion.

We really appreciate your consideration.

Sincerely,

Alexandra Kiss MD

Zoltan Csanadi MD

Comments from the editors and reviewers:

Reviewer #1: The main objective of this clinical study is to assess and quantify the microemboli produced by different ablative catheters and methods in patients that underwent catheter ablation for atrial fibrillation.

The objective is interesting in itself and furthermore because the selected methodology includes PVAC catheters and RF source. It is already known since a few years, how the original PVAC method produce cerebral microemboli.

So the authors using the same ablation protocol of pulmonary vein isolation in all the patients included, compare the incidence and quantify the microemboli and its material solid or aerial, produced with the old and the new technology of PVAC altogether with cryoablation and also with the new system of consecutive RF delivery applied through a new brand irrigated catheter by Biosense Webster.

The epidemiological importance of atrial fibrillation makes of it an important issue, furthermore because many ablated patients today are young and without any other disease. Cerebral microinfarction is then a big issue to be studied.

Concerning the methodology as the authors point out being a single centre study, the numbers of patients in each group are low, to obtain a heavy weight on statistical analysis. Besides it is not a randomized study.

Another limitation is the method selected by the authors of doppler analysis during the procedure of the middle cerebral arteries. Certainly this objective is weaker and should be supplemented by pre and post cerebral MR.

In any case as each methodology could serve as control for the rest, I induce that the results are truly valid. It seems that most of the microemboli are gas and also that the PVAC I, and the new Biosense catheter produce more microemboli than the amended PVAC II and III altogether with cryoablation.

Concerning preablation anticoagulation the authors should state exactly the period it has been prescribed.

**We changed the text in the Methods / Patients section and included this information:**

*"1. Pre-ablation treatment with a vitamin K antagonist (VKA) for a minimum of 3 weeks and a therapeutic (above 2.0) international normalized ratio (INR) confirmed on the day of the procedure, and activated clotting time (ACT) levels above 300 s during ablations."*

The manuscript has some items typed in black and this must be changed.

**We realized that some parts of the text appeared in bold and Italic in the PDF generated during online submission, despite the Word file we submitted did not contain such**

sections. We kindly ask for your technical assistance to solve this problem in case it occurs again during this resubmission.

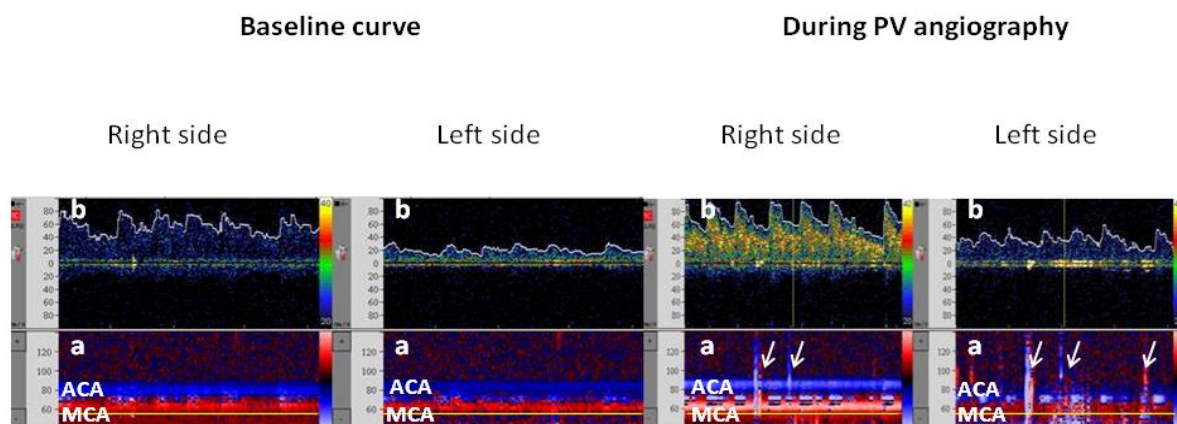
Bibliography is correct and appropriate.

The tables and figures are appropriate but need abbreviations, for any one used in them.

**Complete list of abbreviations were included to all tables and figures in the revised manuscript.**

The figure 1 need a detailed text explaining each of the panels and what is seen in any of them, otherwise it cannot be understood.

**Figure 1 has been reconstructed with arrows and labels for clarification. In addition figure legend has been modified to facilitate interpretation.**



”Bilateral Multifrequency Transcranial Doppler Monitoring of the Middle Cerebral Arteries

(a) Demonstration of beam alignment of both right and left sided MCA and ACA. Continuous yellow line indicates the location of monitoring at 55 mm insonation depth (MCA).

(b) MCA waveform.

Arrows on right panel indicate the high intensity transient signals corresponding to cerebral microemboli during PV angiography.

**MCA**, middle cerebral artery; **ACA**, anterior cerebral artery ”



**Author Agreement Form – International Journal of Cardiology**

Manuscript Title: **Cerebral microembolization during atrial fibrillation ablation:**

**comparison of different single-shot ablation techniques**

List of all Authors: Alexandra Kiss, Edina Nagy-Baló, Gábor Sándorfi, István Édes, Zoltán

Csanádi

Corresponding Author: Alexandra Kiss

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*. We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in IJC 2013 (Shewan LG *et al* 2013 in press).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission.

**Ms. Ref. No.: IJC-D-14-00422**

**Title: Cerebral microembolization during atrial fibrillation ablation: comparison of different single-shot ablation techniques.**

**International Journal of Cardiology**

### **Responses for Reviewer #1**

Comments from the editors and reviewers:

Reviewer #1: The main objective of this clinical study is to assess and quantify the microemboli produced by different ablative catheters and methods in patients that underwent catheter ablation for atrial fibrillation.

The objective is interesting in itself and furthermore because the selected methodology includes PVAC catheters and RF source. It is already known since a few years, how the original PVAC method produce cerebral microemboli.

So the authors using the same ablation protocol of pulmonary vein isolation in all the patients included, compare the incidence and quantify the microemboli and its material solid or aerial, produced with the old and the new technology of PVAC altogether with cryoablation and also with the new system of consecutive RF delivery applied through a new brand irrigated catheter by Biosense Webster.

The epidemiological importance of atrial fibrillation makes of it an important issue, furthermore because many ablated patients today are young and without any other disease. Cerebral microinfarction is then a big issue to be studied.

Concerning the methodology as the authors point out being a single centre study, the numbers of patients in each group are low, to obtain a heavy weight on statistical analysis. Besides it is not a randomized study.

Another limitation is the method selected by the authors of doppler analysis during the procedure of the middle cerebral arteries. Certainly this objective is weaker and should be supplemented by pre and post cerebral MR.

In any case as each methodology could serve as control for the rest, I induce that the results are truly valid. It seems that most of the microemboli are gas and also that the PVAC I, and the new Biosense catheter produce more microemboli that the amended PAVC II and III altogether with cryoablation.

Concerning preablation anticoagulation the authors should state exactly the period it has been prescribed.

**We changed the text in the Methods / Patients section and included this information:**

*”1. Pre-ablation treatment with a vitamin K antagonist (VKA) for a minimum of 3 weeks and a therapeutic (above 2.0) international normalized ratio (INR) confirmed on the day of the procedure, and activated clotting time (ACT) levels above 300 s during ablations.”*

The manuscript has some items typed in black and this must be changed.

**We realized that some parts of the text appeared in bold and Italic in the PDF generated during online submission, despite the Word file we submitted did not contain such sections. We kindly ask for your technical assistance to solve this problem in case it occurs again during this resubmission.**

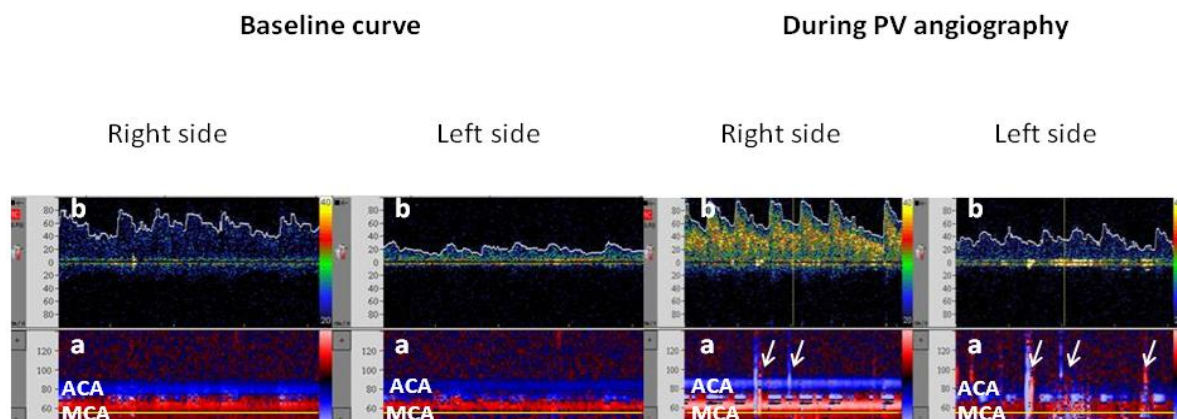
Bibliography is correct and appropriate.

The tables and figures are appropriate but need abbreviations, for any one used in them.

**Complete list of abbreviations were included to all tables and figures in the revised manuscript.**

The figure 1 need a detailed text explaining each of the panels and what is seen in any of them, otherwise it cannot be understood.

**Figure 1 has been reconstructed with arrows and labels for clarification. In addition figure legend has been modified to facilitate interpretation.**



”Bilateral Multifrequency Transcranial Doppler Monitoring of the Middle Cerebral Arteries

(a) Demonstration of beam alignment of both right and left sided MCA and ACA. Continuous yellow line indicates the location of monitoring at 55 mm insonation depth (MCA).



(b) MCA waveform.

Arrows on right panel indicate the high intensity transient signals corresponding to cerebral microemboli during PV angiography.

**MCA**, middle cerebral artery; **ACA**, anterior cerebral artery ”

**Cerebral microembolization during atrial fibrillation ablation:  
comparison of different single-shot ablation techniques**

Alexandra Kiss<sup>1</sup>, Edina Nagy-Baló<sup>1</sup>, Gábor Sándorfi<sup>1</sup>, István Édes<sup>1</sup>, Zoltán Csanádi<sup>1</sup>

Institute of Cardiology, University of Debrecen, Debrecen, Hungary

**Corresponding author:** Alexandra Kiss MD

Address: Institute of Cardiology, University of Debrecen

22 Móricz Zs. Krt.

Debrecen, Hungary

H-4032

Phone: +36304152604

Fax: +3652414928

E-mail: [kiss.alexandra@hotmail.com](mailto:kiss.alexandra@hotmail.com)

**Keywords:** atrial fibrillation, pulmonary vein isolation, transcranial Doppler, cerebral microemboli

<sup>1</sup> This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

## ABSTRACT

**Background:** Clinically silent cerebral ischemia (SCI) detected by diffusion-weighted MRI has been reported in 5-40% of patients undergoing pulmonary vein isolation (PVI). Although initial reports suggested a high rate of SCI with phased radiofrequency (RF) ablation on use of the pulmonary vein ablation catheter (PVAC), the incidence was subsequently markedly reduced in consequence of procedural modifications in recent studies.

We analyzed cerebral microembolization as assessed with transcranial Doppler during phased RF ablation and with two other single-shot AF ablation technologies: the cryoballoon (CB) and the nMARQ™ multipolar irrigated RF ablation system.

**Methods and results:** A total of 89 patients (mean age: 57, SD: 12 years; 62 male) with paroxysmal or persistent AF, underwent PVI. Phased RF was used according to the initial protocol in 7 patients (PVAC Group I), with procedural modifications and a newer (14.4) version of the RF generator in 37 patients (PVAC Group II) and with the most recent (version 15.0) generator in 18 patients (PVAC Group III). Ablation was performed with the CB in 13 and with the nMARQ system in 14 patients.

The number of microemboli (mean+(SD) detected in the middle cerebral arteries was 2703(918) in PVAC Group I, 1087(542) in PVAC Group II, 719(469) in PVAC Group III, 1057(784) with CB and 2166(1047) with nMARQ ( $p<0.01$ ).

**Conclusion:** Significant decreases in MES counts were observed thanks to the procedural modifications and newer RF generator with phased RF. High MES counts comparable to those with the initial phased RF resulted from the use of nMARQ.

## **Introduction**

Pulmonary vein (PV) isolation (PVI) is an established method for the treatment of atrial fibrillation (AF), with a relatively low risk (<1%) of major periprocedural complications, including clinical stroke or transient ischemic attack (TIA) [1]. However, significant concern has been raised regarding the long-term safety of PVI as clinically silent cerebral ischemia (SCI) detected by diffusion-weighted (DW) MRI has been reported in 5-40% of the patients, depending on the ablation technology used [2-8]. Further, the limited data available suggest that a cognitive decline potentially related to SCI can be demonstrated several months after these ablations in some patients. In some studies, a markedly higher incidence of SCI was reported after PVI performed with phased radiofrequency (RF) and the PV ablation catheter (PVAC), as compared with the cryoballoon (CB) or focal irrigated RF ablation [2,3]. More recent reports with phased RF ablation, however, demonstrated a significant decrease in the incidence of SCI, these favourable results were attributed to the use of more rigorous periprocedural anticoagulation protocols and some specific modifications in the procedural technique [9-11]. These procedural changes were based on the results of animal studies [12, 13] and included the avoidance of overlap between 2 electrodes during RF applications and careful sheath management to prevent air embolization. Software modifications refining the power handling of the GENius RF generator have also been implemented.

The recording of microembolic signals (MESs) in the middle cerebral arteries (MCAs) by transcranial Doppler (TCD) has been used to assess microembolization during different cardiovascular procedures [14-16]. Although DW MRI is regarded as the gold standard for the demonstration of cerebral lesions post-ablation, recording of the MESs provides a unique opportunity through which to monitor the intensity of microembolus generation during different phases of the procedure. In line with the initial DW MRI results, when we used the

earlier version of the GENius generator we detected a significantly higher number of MESs during ablation with the PVAC as compared with the CB [17]. Further, we demonstrated that the majority of the microemboli were generated during the energy delivery (ED) with phased RF ablations, while the rate of microembolization was relatively uniform throughout the procedure with the CB. Whether the procedural and technical modifications which decreased lesion formation on DW MRI with the phased RF technology would also reduce the microembolization detected by TCD is unknown.

Phased RF ablations with the PVAC have been performed for 5 years in our center, using subsequent versions of the GENius RF generator together with specific procedural modifications to improve safety as suggested by the literature data. MESs are detected with TCD routinely during all AF procedures in our laboratory. In this study, we analysed our TCD data obtained with phased RF ablations in relation to the procedural changes implemented in recent years. In order to view these results in context with other single-shot AF ablation technologies designed for fast and simplified PVI, we have compared the MES data with those obtained by using the CB and the novel nMARQ<sup>TM</sup> (Biosense Webster, Inc., Diamond Bar, CA, USA) multipolar irrigated RF ablation system.

## **Methods**

### ***Patients***

Consecutive patients undergoing PVI for symptomatic paroxysmal or persistent AF not adequately controlled by at least one antiarrhythmic drug were considered for inclusion in the study. Exclusion criteria included 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  $\leq 40\%$ , 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, a contraindication to oral anticoagulation and pregnancy. All participating patients provided their signed informed consent prior to the procedure.

Further prerequisites for inclusion in this study were as follows:

1. Pre-ablation treatment with a vitamin K antagonist (VKA) **for a minimum of 3 weeks** and a therapeutic (above 2.0) international normalized ratio (INR) confirmed on the day of the procedure, and activated clotting time (ACT) levels above 300 s during ablations.
2. Bi- or unilateral TCD recordings of sufficient quality of the Middle Cerebral Artery (MCA) throughout the LA access period.
3. Ablation performed with one of 3 single-shot technologies designed for PVI: phased RF, CB or nMARQ. As PVI with phased RF and the PVAC was performed with the use of 3 different versions of the GENius generator, and this was also accompanied by significant procedural modifications, the MES data acquired with this technology were analyzed separately in 3 treatment groups (PVAC Groups I, II and III).

### ***Pre-ablation evaluation and LA catheterization***

Patients were admitted to the hospital 1 or 2 days prior to the procedure. Transesophageal echocardiography was performed to exclude the presence of an intracardiac

thrombus within 24 h before the ablation. All patients received oral anticoagulation before the PVI, with a target INR of 2.0 to 3.0.

All 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, or in some cases under intracardiac echocardiographic (ICE) guidance, using a Brockenbrough needle (St. Jude, Inc., Zaventem, Belgium) and a Swartz sheath (St. Jude, Zaventem, Belgium). This sheath was exchanged for the deflectable 12 Fr FlexCath sheath (Medtronic CryoCath LP, Kirkland, Quebec, Canada), which was flushed continuously with heparinized saline, and which was used with any of the ablation catheters utilized in this study. 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. Additional 2000-5000 IU iv boluses of heparin were administered as needed to attain the minimum target ACT level.

### ***Ablation techniques***

#### *Phased RF ablation*

The technical specifications of the PVAC and the GENius RF generator (Medtronic Inc., Minneapolis, MN, USA) have been described in detail [17-20]. The catheter was advanced through the FlexCath sheath over a 0.032-inch guidewire (BARD

Electrophysiology Inc., Lowell, MA, USA), which was positioned selectively in 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 application at each PV, the positions of the electrodes relative to the PV ostium were always confirmed by means of contrast injection through the FlexCath sheath. Care was always taken to apply the RF outside the PV in the antral region, targeting potentials of high amplitude on as many electrodes as possible for each application. RF energy was applied for 60 s, usually 3-4 times per PV, until PVI was achieved. The target temperature was 60 °C, measured separately for all bipoles. Any electrode pair that failed to reach at least 50 °C during RF delivery was switched off to avoid ineffective ED due to improper contact at the electrode-tissue interface. Common ostia were isolated by inserting the guidewire into the different side branches and ablating subsequent segments of the targeted veins. The PV conduction was reassessed after each RF application, the electrodes being advanced inside the ostium. The endpoint of the procedure was the electrical isolation of all PVs, as confirmed by an entrance block.

The GENius RF generator is capable of delivering RF in a duty-cycled mode with different bipolar/unipolar ratios to any or all of the electrodes on the PVAC. Three consecutive versions of the GENius RF generator (Medtronic Inc. , Minneapolis, MN, USA) were used in the course of recent years, also coupled with some procedural modifications as follows:

1. *PVAC Group I.* Initial series of ablations were performed with the use of software version 14.3 for the GENius generator. Bipolar/unipolar RF application was started at a ratio of 4:1 for each PV and changed to a bipolar/unipolar ratio of 2:1 for a deeper lesion when a sufficient reduction in local electrogram amplitude could not be achieved after multiple RF



deliveries. No attempts were made to avoid the potential interaction between the first and the last electrode (E1-E10) in the PVAC.

2. *PVAC Group II.* Ablations were performed with software version 14.4 for the *GENius* generator. Modifications in the procedural technique were implemented in this group of patients as follows. Potential interaction between the most distal (E1) and the most proximal (E10) electrodes was considered and simultaneous EDs on these poles were attempted only after fluoroscopic assessment of the interelectrode distance, which was considered adequate if the space between E1 and E10 was at least double the fixed 3-mm interelectrode distance as assessed from multiple projections. Furthermore, ablations were started in the 2:1 mode and changed to 1:1 in those rare instances when adequate amplitude change and PVI could not be achieved after multiple RF applications. In addition, the distal circular segment of the PVAC catheter was submerged and captured by the introduction device in a saline bath prior to insertion into the FlexCath sheath. This maneuver was used to prevent air entrapment around the array and the introduction of air into the LA through the transseptal sheath.

3. *PVAC Group III.* Ablations were performed using the most recent software version (15.0) for the *GENius* generator. RF delivery to E10 is not supported by this software thereby excluding the possibility of E1-E10 interaction. No procedural modifications as compared to those in PVAC Group II. were implemented during these ablations.

### **CB ablation**

The technology of CB ablation has been described in detail [17]. In brief, a 28-mm CB was used in all cases. The CB was introduced into the PV ostium over an inner lumen

mapping catheter (Achieve, Medtronic Ablation Frontiers LCC, Carlsbad, CA, USA) which is capable of mapping PV potentials before, during and after cryo applications. The best possible occlusion of the PVs was facilitated by the steerable sheath and by positioning the guidewire in a PV branch to provide maximal support. Furthermore, all special maneuvers described previously, such as the “pull-down” or the “hockey stick” techniques, were used as needed [21].

PV occlusion was assessed by means of a hand-held injection of contrast medium (Optiray Covidien Deutschland GmbH, Neustadt/Donau, Germany) through the injection side-port of the Arctic Front catheter. A minimum of two 5-min freezing cycles were applied per PV. The balloon was repositioned for each application, preferably with the guidewire situated in a different branch of the PV in order to maximize the effect of freezing at different aspects of the ostium. Before the start of ablation of the septal veins, a quadripolar catheter was placed in the superior caval vein, where constant capture of the right phrenic nerve could be achieved. One stimulus at maximal output was delivered every 5 s, with manual assessment of the diaphragmatic movement. The freezing cycle was terminated immediately if loss or weakening of the diaphragm response occurred. PVI was assessed on the basis of the signals recorded by the Achieve wire.

### **nMARQ ablation**

*The nMARQ™ (Biosense Webster, Inc., Diamond Bar, CA, USA) is a multi-electrode, irrigated RF ablation catheter with a uni-directional deflectable tip. The distal tip section is circular or semilunar and contains 10 platinum ring electrodes with irrigation holes at both ends for stimulation, recording and ablation. The diameter of the circular or*

*semilunar loop is variable to accommodate the LA anatomy.* The catheter is integrated with the CARTO 3 electroanatomical mapping system, which provides mapping and real-time navigation capabilities. *For ablation, the catheter is used in conjunction with the nMARQ™ Multi-Channel RF Generator, which is able to deliver RF simultaneously to multiple electrodes in unipolar or bipolar mode.*

*The circular-tip catheter was used exclusively in this study. The catheter was advanced to the LA through the FlexCath guiding sheath. The 3-dimensional map of the LA was constructed by using the CARTO™ electroanatomical mapping system (Biosense Webster, Inc., Diamond Bar, CA, USA) equipped with Cartomerge™ software (Biosense Webster, Inc., Diamond Bar, CA, USA). The pre-ablation cardiac CT image of the LA with the proximal portions of the PVs was imported and registered for real-time mapping, focusing on the PVs and the PV antra of the LA. In addition, the positions of the electrodes relative to the PV ostium were always confirmed before the first RF application at each PV, by means of contrast injection through the FlexCath sheath. Care was taken to apply the RF outside the PV in the antral region, targeting potentials of high amplitude on as many electrodes as possible for each application. RF energy was applied for up to a maximum of 60 s at a maximum of 20 W/electrode in the unipolar mode, with the target temperature set at 43 °C. Electrodes not demonstrating the desired rise in temperature up to 40 °C during energy delivery were switched off. The irrigation flow rate between RF applications was 4 ml/min, which was increased to **60 ml/min, starting 5 s before the onset of RF application and maintained until 5 s after termination.** The electrical conduction properties of the PVs were assessed via the recordings through the electrodes of the nMARQ catheter. The endpoint of the procedure was the electrical isolation of all PVs, as confirmed by an entrance block.*

### ***TCD recording and evaluation of the MES count***

TCD recording was performed throughout the whole period of LA access (from the transseptal puncture to the removal of all catheters and sheaths from the LA). The transducer was held in place by a proprietary headpiece supplied with the system. The MCAs were bilaterally insonated from transtemporal windows by using a multifrequency Doppler (Multi Dop T digital, DWL, QL software 2.8) which insonates simultaneously with frequencies of 2 and 2.5 MHz. The system is capable of the automatic online identification of true MESs with a sensitivity of 100% and a specificity of 99.3% [22], and also of discrimination between gaseous and solid emboli with a specificity of 96.5%[23]. The identification of true MESs with parallel artefact rejection is possible by implementing an event detector system, using a previously published algorithm to detect high-intensity signals due to emboli[22]. This step is followed by a second algorithm using data from the dual-frequency insonation to determine whether the MESs are to be attributed to a solid or to a gaseous embolus. Differentiation is possible because the reflection of ultrasound power is dependent not only on the size of the embolus, but also on its composition and the insonating frequency used: solid emboli reflect more ultrasound at 2 MHz than at 2.5 MHz, whereas the opposite is true for gaseous emboli. TCD parameter settings as recommended by the consensus criteria [24] were kept constant during the procedures. The insonation depth was 45-55 mm, the sample volume was 8 mm, and the power was 60-100 mW. An example of a TCD record is given in Figure 1. MES counts were collected and evaluated separately during different stages of the procedure, as follows:

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

2. PV angiography: contrast injection through the injection port of the CryoCath catheter or the transseptal sheath during PVAC or nMARQ ablation.
3. Energy delivery: from the start until 15 s after the termination of ED
4. The remainder of the procedure: that part of the LA access period during which none of the aforementioned maneuvers were performed.

As bilateral insonation of the MCA could not be achieved in all patients for technical reasons, the results were provided as MES count per MCA, i.e. either the mean of bilateral recordings or the number from the unilateral recording.

### ***Statistical analyses***

Statistical analysis was performed by using IBM SPSS 20. Data are reported as means and standard deviation (SD). In the case of Figure 1, data are shown as mean and 95% confidence intervals (95% CI). The normality of continuous variables was evaluated by means of the Kolmogorov- Smirnov test. Statistical differences between groups were determined by using analysis of variance when the data showed normal distribution and homoscedasticity (Levene's statistic); otherwise, the Kruskal-Wallis test was performed. For comparison of the MES counts obtained during CB ablation versus those during the other 4 techniques, the Mann-Whitney test was used. In all statistical tests a p value below 0.05 was considered as significant.

### **Results**

### *Patient characteristics*

A total of 89 patients were enrolled in the study. Demographic and clinical parameters on the patients in the 5 treatment groups are presented in Table 1. There were no significant intergroup differences in the baseline characteristics.

### *Procedural data*

Procedural data are listed in Table 2. The total procedure, fluoroscopy, ED and LA access times demonstrated significant differences. The acute success rates were 100% in the 3 PVAC Groups, and 98% in both the CB and the nMARQ groups. The shortest LA access time was achieved in PVAC Group III, while the shortest ED time was obtained during ablation with the nMARQ. There were no significant differences between the intraprocedural ACT values. Symptomatic thromboembolic event did not occur in any patient.

### *MES counts*

The MES count detected with the CB was used as a reference for comparison with the other technologies (Figure 2, left panel). No significant difference was found between the CB group, PVAC Group II ( $p=0.543$ ) and PVAC Group III ( $p=0.317$ ) in the total cerebral MES counts. However significantly higher MES counts were demonstrated in PVAC Group I ( $p=0.005$ ) and with the nMARQ technique ( $p=0.007$ ). The ratios of gaseous versus solid MESs detected in the 5 treatment groups did not differ significantly ( $p=0.688$ ). (Figure 2, right panel)

The distribution of the MES counts during different stages of the procedure is depicted in Figure 3. A relatively even distribution of embolus formation was observed across the whole LA access time in the CB group, and in PVAC Groups II and III, whereas, microemboli were detected mostly during ED in PVAC Group III and with nMARQ.

## **Discussion**

Major differences have been reported in the incidence of SCI after AF ablation with various technologies and with the different methods and criteria applied to evaluate cerebral lesions. The diversity of the periprocedural anticoagulation routine in the various studies further hampers a direct comparison of the different AF ablation techniques. In the present study, we compared different single-shot ablation tools designed for PVI without additional LA ablation (eg. creating long linear lesions, or ablating complex fractionated electrograms) in patients with similar baseline characteristics. Further, periprocedural anticoagulation was homogeneous across all treatment groups with uninterrupted VKA administration and therapeutic INR level before the procedure and iv heparinization to a target ACT above 300 s in agreement with current recommendations [25]. Any differences demonstrated in the number of microemboli are therefore truly inherent to the ablation techniques compared.

The rate of microembolization during phased RF ablation with the implementation of specific procedural modifications and the use of consecutive software versions of the GENius generator demonstrated a significant decrease in our study. The very same trend was observed in recent DW MRI studies on the rate of new SCI lesions after phased RF ablation. Importantly, no difference was detected in the level of microembolization between the procedure with CB ablation versus that with the PVAC after procedural and software changes

had been implemented (PVAC Groups II and III). In contrast, significantly higher MES counts were recorded during phased RF ablation with the use of the old technique (PVAC Group I) and during ablation with nMARQ (Figure 2).

The significant reduction in microembolization with phased RF was clearly related to the elimination of the MESs during the ED period of the procedure. Similarly to as observed in PVAC Group I, the majority of the microemboli were generated during ED with nMARQ, which also represents a multielectrode RF ablation technology (Figure 3). It is noteworthy that MESs were largely gaseous in nature in all treatment groups.

#### ***Measures related to the reduction in cerebral embolization with phased RF ablation***

The significant reduction achieved in clinically silent microembolization, as demonstrated by DW MRI studies and our own results, were related to refinements in specific technical elements of the phased RF ablation, based on preclinical data [12,13]. The observation of enhanced microembolization with blended unipolar:bipolar energy delivered through PVAC electrodes in close proximity to each other was of utmost importance. While this problem remained unknown, this was a likely common scenario, owing to the squeezed situation of the distal PVAC loop. It should be noted that actual physical contact between any two electrodes results in an electrical short circuit and immediate termination of the RF delivery. On the other hand, not contact, but a reduced interelectrode space (less than the fixed 3 mm between two neighboring electrodes mounted on the distal circular segment of the PVAC) may lead to blood and tissue overheating, due to a high current density. Simple measures to avoid this possibility include a careful fluoroscopic assessment of the electrode positions (as we did in PVAC Group II), exclusion of simultaneous RF ED to electrodes 1 and



10, as proposed by several authors [9-12] and a software modification implemented in the latest version of the GENius generator, which supports simultaneous RF delivery to a maximum of 9 electrodes (software version 15.0; PVAC Group III in our study).

The earlier practice of starting ED in a 4:1 bipolar:unipolar mode at each PV was changed to start with a 2:1 ratio in PVAC Groups II and III. The rationale for this change was to avoid extensive bipolar ED and thereby reduce local heating between adjacent electrodes. Although animal data suggested a tendency for more microemboli with more bipolar RF delivery, the contribution of this change in the reduction of microemboli is uncertain. Nonetheless, starting with the 2:1 instead of the 4:1 ratio is the current practice at other centers [9-11,26].

As demonstrated in an animal model, a potential source of gaseous emboli was the introduction of air into the LA via the transseptal sheath. A significantly larger air volume was measured during the introduction of the PVAC, possibly owing to its more complex shape as compared with a conventional focal RF catheter. To prevent air entrapment around the array, the PVAC was submerged and captured by the introduction device in a saline bath prior to insertion into the FlexCath sheath.

It is noteworthy that, in addition to the procedural changes as described above, the GENius RF generator has also been modified in recent years. An improved energy titration algorithm was implemented starting at version 14.4 (PVAC Group II), which regulates the power delivery to control the maximum, instead of the average temperature, with a target of 60 °C. Further, this software ensures a gradual and limited increase (4 W/s) during variable or intermittent electrode-tissue contact, to avoid high temperature peaks. The importance of the catheter-tissue contact has been highlighted since the introduction of contact force measurement for focal RF ablation catheters [27,28]. With multipolar ablation, this becomes even more critical, as the maintenance of good contact simultaneously on multiple electrodes

can be challenging and the capability of direct contact force measurement with this technology is not yet available. This concept is supported by our previous study: with an analysis of temperature and power data obtained at high resolution sampling from the GENius generator, increased microembolus formation was demonstrated during intermittent contact scenarios when low temperature was compensated by increased power which resulted in a temperature overshoot when the contact was re-established [29]. The latest issue of the GENius software (15.0; PVAC Group III) features the energy titration algorithm of version 14.4, and in addition, RF delivery is limited to 9 electrodes, thereby providing a definite solution for the problem of E1-E10 interaction.

### ***Microembolization during CB and nMARQ***

**The use of cryoenergy is generally regarded as a more “tissue-friendly” and safer ablation technology, which is associated with a significantly lower incidence of thrombus formation as compared with RF ablation [30]. The limited data available on microembolus generation with CB ablation demonstrated consistent results. The total MES count during CB ablation in the present study (1057 SD: 784) was reasonably similar (834 SD: 727) to that recorded in our previous work [17], and to that reported by Sauren et al. (935 SD: 463 ) [31]. Importantly, we also demonstrated that the microemboli were predominantly gaseous, with an even distribution throughout the LA access period. It should be noted that results obtained on SCI with different AF ablation technologies as evaluated with DW MRI are in agreement with these TCD data)[3].**

**Although the results obtained with the nMARQ ablation system reflect our initial experience, we found this technology to be very effective with the shortest ED time**

required for acutely successful PVI in this study. However, this technology was also associated with a high rate of microembolization, of the magnitude of that initially achieved with phased RF (PVAC Group I), and significantly higher than the numbers obtained with modified phased RF (PVAC Groups II and III) and with CB. Recently published results of a German center [32] seem to support our findings: DW MRI demonstrated SCI acutely in 14 (33%) out of 43 patients after PVI with the nMARQ catheter, a ratio similar to the values up to 39% [2,6] in earlier reports on phased RF ablation.

The high microembolization rate was somewhat unexpected after the earlier experience demonstrating lower incidence of SCI [3] and lower microembolus counts [31] with focal irrigated as compared with conventional RF ablation. As a potential explanation, one speculative possibility is the irrigation itself used with the nMARQ catheter, with a very high rate of 60 ml/min during ED. Direct injection of saline into the LA at this rate is known to result in marked bubble formation due to cavitation [33], which is readily visible on ICE (as we observed in cases when ICE was used during ablations). This mechanism could be responsible for a currently unknown proportion of cerebral microemboli. These microemboli are gaseous, which are generally considered to be less harmful than solid particles, although their significance in the long-term cognitive function is yet to be determined. Other possible causes are likely to be inherent to multielectrode ablation and the high total energy delivered when this catheter is used. By analyzing biophysical parameters during phased RF ablation [28], our group earlier demonstrated that microemboli generation was related to both the number of active electrodes during ED and the total energy delivered. Further, maintenance of a good contact on multiple poles throughout the entire duration of RF applications might be challenging, and power handling in intermittent contact scenarios could therefore be of

**significance. There is an urgent need for more data on embolization rates and in-depth investigations into the mechanism with the nMARQ system with the aim of making this otherwise promising technology safer.**

### **Limitations**

**This was a single-center investigation on a limited number of patients. The study was non-randomized and the data were analysed retrospectively. However, this methodology did ensure that the patient characteristics and periprocedural anticoagulation were homogeneous, and differences in microembolization therefore represented true differences inherent to the ablation techniques compared.**

### **Conclusions**

A significant decrease in the number of microemboli was demonstrated when phased RF ablation was implemented with specific procedural modifications with the use of newer generations of the GENius RF generator. Microembolus counts were reduced to a level comparable with that observed during CB ablation. A significantly higher microembolization rate, similar to that recorded with the first version of the GENius generator, was demonstrated with the multipolar irrigated nMARQ RF ablation system.

## References

1. Kok LC, Mangrum JM, Haines DE, Mounsey JP. Cerebrovascular complication associated with pulmonary vein ablation. *J Cardiovasc Electrophysiol*. 2002 Aug;13(8):764-7.
2. Herrera Siklódy C, Deneke T, Hocini M, et al. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. *J Am Coll Cardiol*. 2011 Aug 9;58(7):681-8. doi: 10.1016/j.jacc.2011.04.010. Epub 2011 Jun 12.
3. Gaita F, Leclercq JF, Schumacher B, et al. Incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation may change according to technology used: comparison of irrigated radiofrequency, multipolar nonirrigated catheter and cryoballoon. *J Cardiovasc Electrophysiol*. 2011 Sep;22(9):961-8.
4. Schwarz N, Kuniss M, Nedelmann M, et al. Neuropsychological decline after catheter ablation of atrial fibrillation. *Heart Rhythm*. 2010 Dec;7(12):1761-7.
5. Neumann T, Kuniss M, Conradi G, et al. MEDAFI-Trial (Micro-embolization during ablation of atrial fibrillation): comparison of pulmonary vein isolation using cryoballoon technique vs. radiofrequency energy. *Europace*. 2011 Jan;13(1):37-44.
6. Gaita F, Caponi D, Pianelli M, et al. Radiofrequency catheter ablation of atrial fibrillation: a cause of silent thromboembolism? *Magnetic resonance imaging*

assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. *Circulation*. 2010 Oct 26;122(17):1667-73.

7. Schrickel JW, Lickfett L, Lewalter T, et al. Incidence and predictors of silent cerebral embolism during pulmonary vein catheter ablation for atrial fibrillation. *Europace*. 2010 Jan;12(1):52-7.
8. Lickfett L, Hackenbroch M, Lewalter T, et al. Cerebral diffusion-weighted magnetic resonance imaging: a tool to monitor the thrombogenicity of left atrial catheter ablation. *J Cardiovasc Electrophysiol*. 2006 Jan;17(1):1-7.
9. Verma A, Debruyne P, Nardi S, et al. 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. *Circ Arrhythm Electrophysiol*. 2013 Oct;6(5):835-42.
10. Wiczorek M, Hoeltgen R, Brueck M. Does the number of simultaneously activated electrodes during phased RF multielectrode ablation of atrial fibrillation influence the incidence of silent cerebral microembolism? *Heart Rhythm*. 2013 Jul;10(7):953-9.
11. Wiczorek M, Lukat M, Hoeltgen R, et al. Investigation into causes of abnormal cerebral MRI findings following PVAC duty-cycled, phased RF ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2013 Feb;24(2):121-8.
12. Haines DE, Stewart MT, Dahlberg S, et al. Microembolism and catheter ablation I: a comparison of irrigated radiofrequency and multielectrode-phased

radiofrequency catheter ablation of pulmonary vein ostia. *Circ Arrhythm Electrophysiol.* 2013 Feb;6(1):16-22.

13. Haines DE, Stewart MT, Barka ND, et al. Microembolism and catheter ablation II: effects of cerebral microemboli injection in a canine model. *Circ Arrhythm Electrophysiol.* 2013 Feb;6(1):23-30.

14. Borger MA, Peniston CM, Weisel RD, Vasiliou M, Green RE, Feindel CM. Neuropsychologic impairment after coronary bypass surgery: Effect of gaseous microemboli during perfusionist interventions. *J Thorac Cardiovasc Surg.* 2001;121:743-749.

15. Gaunt ME, Martin PJ, Smith JL, Rimmer T, Cherryman G, Ratliff DA, Bell PR, Naylor AR. Clinical relevance of intraoperative embolization detected by transcranial doppler ultrasonography during carotid endarterectomy: A prospective study of 100 patients. *Br J Surg.* 1994;81:1435-1439.

16. Kilicaslan F, Verma A, Saad E, et al. Transcranial Doppler detection of microembolic signals during pulmonary vein antrum isolation: implications for titration of radiofrequency energy. *J Cardiovasc Electrophysiol.* 2006 May;17(5):495-501.

17. Nagy-Baló E, Tint D, Clemens M, et al. Transcranial measurement of cerebral microembolic signals during pulmonary vein isolation: a comparison of two ablation techniques. *Circ Arrhythm Electrophysiol.* 2013 Jun;6(3):473-80.

18. Boersma LV, Wijffels MC, Oral H, Wever EF, Morady F. Pulmonary vein isolation by duty-cycled bipolar and unipolar radiofrequency energy with a multielectrodeablation catheter. *Heart Rhythm*. 2008 Dec;5(12):1635-42.
19. Scharf C, Boersma L, Davies W, et al. Ablation of persistent atrial fibrillation using multielectrode catheters and duty-cycled radiofrequency energy. *J Am Coll Cardiol*. 2009 Oct 6;54(15):1450-6.
20. Boersma L, Duytschaever M, Geller JC, Scharf C. *The PVAC Workbook Remedica*, 2010
21. Chun KR, Schmidt B, Metzner A, et al. The 'single big cryoballoon' technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. *Eur Heart J*. 2009 Mar;30(6):699-709.
22. Russel D, Brucher R. Online automatic discrimination between solid and gaseous microemboli with the first multifrequency transcranial Doppler. *Stroke*. 2002 Aug; 33(8):1975-80
23. Markus HS, Punter M. Can transcranial Doppler discriminate between solid and gaseous microemboli? Assessment of a dual-frequency transducer system. *Stroke*. 2005 Aug; 36(8):1731-4.
24. Ringelstein EB, Droste DW, Babikian VL, et al. Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. *Stroke*. 1998; 29:725-729.



25. Calkins, H., Kuck, K. H., Cappato, R., et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. *Journal of Interventional Cardiac Electrophysiology*, 33, 171–257.
26. Deneke T, Shin DI, Balta O, Postablation asymptomatic cerebral lesions: long-term follow-up using magnetic resonance imaging. *Heart Rhythm*. 2011 Nov;8(11):1705-11.
27. Neuzil P, Reddy VY, Kautzner J, et al. Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study. *Circ Arrhythm Electrophysiol*. 2013 Apr;6(2):327-33.
28. Kuck KH, Reddy VY, Schmidt B, et al. A novel radiofrequency ablation catheter using contact force sensing: Toccata study. *Heart Rhythm*. 2012 Jan;9(1):18-23.
29. Nagy-Balo E, Kiss A, Condie C, Stewart M, Edes I, Csanadi Z. Biophysical background of cerebral microembolization during phased radiofrequency ablation of atrial fibrillation: analysis of high resolution data from the ablation generator. *European Heart Journal*. 2013 34 ( Abstract Supplement ), 1096-1097

30. Khairy P, Chauvet P, Lehmann J, et al. Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. *Circulation*. 2003 Apr 22;107(15):2045-50.
31. Sauren LD, VAN Belle Y, DE Roy L, et al. Transcranial measurement of cerebral microembolic signals during endocardial pulmonary vein isolation: comparison of three different ablation techniques. *J Cardiovasc Electrophysiol*. 2009 Oct;20(10):1102-7.
32. Deneke T, Schade A, Müller P, et al. Acute Safety and Efficacy of a Novel Multipolar Irrigated Radiofrequency Ablation Catheter for Pulmonary Vein Isolation. *J Cardiovasc Electrophysiol*. 2013 Nov 14. doi: 10.1111/jce.12316. [Epub ahead of print]
33. Csanadi Z, Nagy-Baló E, Dank S, et al. Cerebrovascular Complications Related to Atrial Fibrillation Ablation and Strategies for Periprocedural Stroke Prevention. *Cardiac Electrophysiol Clinics* 2014; March (in press) DOI: 10.1016/j.ccep.2013.10.003

**TABLE**

**Table 1. Patient clinical characteristics**

<b>Variable</b>	<b>CB</b>	<b>PVAC I.</b>	<b>PVAC II.</b>	<b>PVAC III.</b>	<b>nMARQ</b>	<b>p</b>
	<b>n=13</b>	<b>n=7</b>	<b>n=37</b>	<b>n=18</b>	<b>n=14</b>	
<b>Age, years (SD)</b>	57(15)	54(8)	60(10)	55(12)	53(12)	0.372
<b>Male, n (%)</b>	9 (69)	6(85)	25(67.5)	12(67)	10(71)	
<b>Type of AF</b>						
Paroxysmal AF, <i>n (%)</i>	11(84)	6(85)	25(67.5)	12(67)	10(71)	
Persistent AF, <i>n (%)</i>	2(16)	1(15)	12(32.5)	6(33)	4(29)	
<b>Arterial hypertension, n (%)</b>	7(53)	2(28)	28(75)	13(72)	8(57)	
<b>Diabetes mellitus, n (%)</b>	0(0)	2(28)	3(8)	1(5.5)	1(7)	
<b>LA short diameter, mm (SD)</b>	41(4)	40(4)	42(3.5)	43(6)	42(3.7)	0.825
<b>LVEF, % (SD)</b>	55(4)	52(8)	55(5)	54(10)	58(5)	0.325
<b>Mean CHADS<sub>2</sub> score</b>	0.62	0.71	0.92	0.83	0.64	0.491
<b>Mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>	1.23	0.86	1.65	1.39	1.14	0.309

AF, atrial fibrillation; EF, ejection fraction; LA, left atrial; LV, left ventricular; **CB**, cryoballoon; **PVAC**, pulmonary vein ablation catheter;

**Table 2. Procedural parameters**

<b>Procedural parameters</b>	<b>CB n=13</b>	<b>PVAC I n=7</b>	<b>PVAC II n=37</b>	<b>PVAC III n=18</b>	<b>nMARQ n=14</b>	<b>p</b>
<b>Total procedure time(min)(SD)</b>	126 (24)	89 (23)	88 (16)	86(25)	108 (25)	<0.001
<b>Fluoroscopy time (min) (SD)</b>	28.8 (8)	17.7 (8.4)	21.2 (8.8)	16.5 (5.3)	21.1(7.8)	0.002
<b>Energy delivery time (min) (SD)</b>	34.2 (18.8)	16 (4.5)	14.9 (4.1)	12(2.8)	7.7(3.4)	<0.001
<b>Left atrial access time (min) (SD)</b>	80.8 (26)	70.4(22.7)	55.4 (15.1)	47.2(13.6)	75.9 (27.4)	<0.001
<b>Intraprocedural ACT (s)</b>	340	380	358	328	317	0.148
<b>Acute success rate (% of isolated PVs)</b>	98	100	100	100	98	

**PV**, pulmonary vein; **other abbreviations as above**

## FIGURE LEGENDS

**Figure 1. Bilateral Multifrequency Transcranial Doppler Monitoring of the Middle Cerebral Arteries**

(a) Demonstration of beam alignment of both right and left sided MCA and ACA. Continuous yellow line indicates the location of monitoring at 55 mm insonation depth (MCA).

(b) MCA waveform.

Arrows on right panel indicate the high intensity transient signals corresponding to cerebral microemboli during PV angiography.

**MCA**, middle cerebral artery; **ACA**, anterior cerebral artery

**Figure 2. Left panel:** Total Microembolic Signal Count in the Five Treatment Groups. A plot of the mean number of microembolic signals (MESs) per middle cerebral artery in each treatment group, as compared with the CB group.

**Right panel:** Ratio of Gaseous/Solid Emboli in the Five Treatment Groups.

(Abbreviations as in tables)

**Figure 3. Microembolic Signal Counts During Different Stages of the Procedure.**

(Abbreviations as above)



**Figure 1**  
[Click here to download high resolution image](#)

**Baseline curve**

**During PV angiography**

Right side

Left side

Right side

Left side

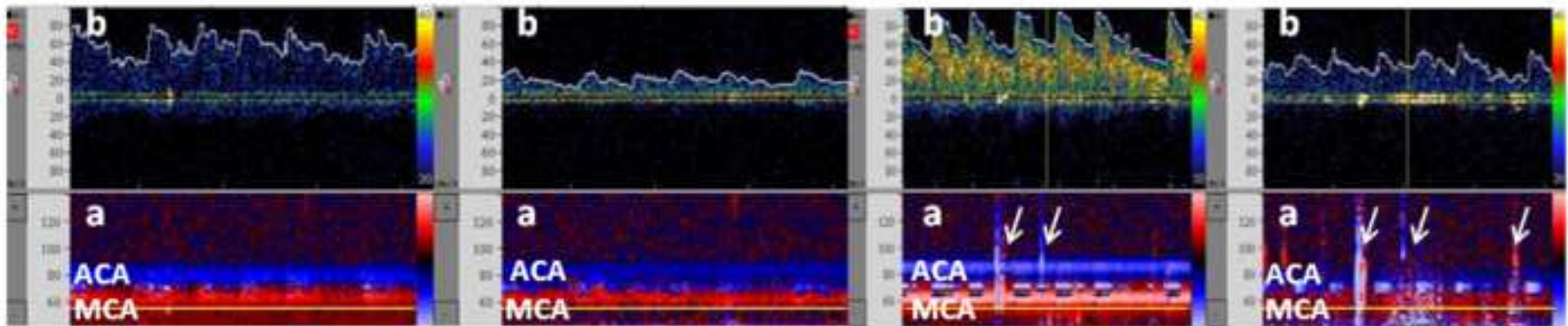


Figure 2  
[Click here to download high resolution image](#)

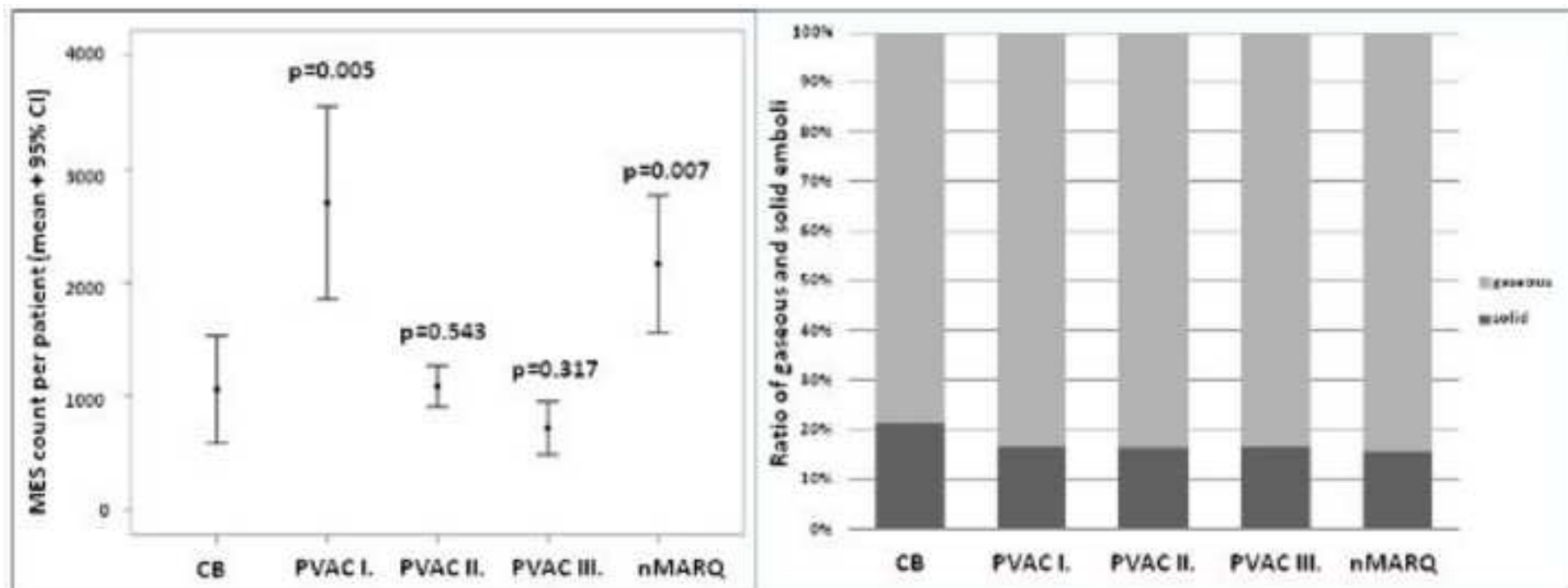




Figure 3  
[Click here to download high resolution image](#)

