Phased RF Ablation: Results and Concerns

Alexandra Kiss, MD, PhD, Gábor Sándorfi, MD, Edina Nagy-Baló, MD, PhD, Mihran Martirosyan, MD, Zoltan Csanadi, MD, PhD

Department of Cardiology, University of Debrecen, Debrecen, Hungary.

Abstract

Treatment of atrial fibrillation (AF) with catheter ablation has proven to be a safe and effective treatment modality which is offered to an increasing number of patients in many centers. Pulmonary vein isolation (PVI) is an established cornerstone of AF ablation strategies. Athough the isolation of the pulmonary veins (PVs) with irrigated focal radiofrequency (RF) catheters using a point-by-point method is considered as the gold standard, it can be challenging to create contiguous lesions, time consuming, and require advanced three dimensional (3D) mapping and navigational systems. The phased RF ablation system was designed to address many of these challenges associated with conventional focal RF ablation. In this review, we describe the main features of phased RF ablation and summarize the data available on clinical outcome with this technology.

Introduction

Catheter ablation for AF has emerged as an alternative to antiarrhythmic drug (AAD) therapy after the failure of at least one AAD, or even as the first line of treatment in selected cases.[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 PVs. This is currently most commonly achieved by encircling the PVs with focal RF lesions under the guidance of a 3D electroanatomical mapping or navigation system.[4] This point-by-point ablation technique requires extensive operator experience for efficiency and safety, and is usually associated with long procedure times, especially in centers with limited experience. Novel methods aiming at simpler and faster PVI have therefore been developed in recent years, including balloon-based technologies.

Cryoballoon (CB) ablation was the first introduced[5-6] and continues to be utilized routinely in many centers. The laser balloon has also been accepted and is becoming used increasingly in even more laboratories.[7] Only limited clinical data are available with the "hot" RF balloon,[8] while the high-intensity focused ultrasound balloon has been removed from clinical practice after lethal complications.[9] The common concept of these "single-shot" AF ablation technologies is the creation of circular lesions for PVI by placing the ablation device at the antrum or ostium of the PVs without the need for continuous repositioning.

Disclosures:
None.

Corresponding Author:
Dr. Zoltan Csanadi
22 Móricz, Debrecen
H-4032, Hungary.

The phased RF ablation system was also designed to address many of the challenges associated with conventional focal catheter ablation. Specifically, the system utilizes anatomically designed, multi-electrode catheters with tissue temperature monitoring and a closed-loop power control generator to create contiguous, transmural lesions.[10]

Phased RF Ablation Technique

The phased RF AF ablation catheter family consists of 3 catheters (Fig. 1).

The circular multipolar pulmomary vein ablation catheter (PVAC; Medtronic Inc, Minneapolis, MN, USA) was designed to create antral lesions of the PVs and provide distal mapping and pacing to assess PVI. The original version of the PVAC consisted of a 25-mm helical electrode array with 10 platinum electrodes and over-the-wire tracking for enhanced PV targeting and placement stability. Most of the published data reflect the experience with this device, which was recently replaced by the PVAC Gold catheter which contains 9 gold electrodes. Gold has more than 4 times better thermal conductivity than that of platinum, thereby providing faster cooling and more precise temperature control. The number of electrodes was reduced in order to eliminate the potential bipolar short circuit between electrodes 1 and 10, which did occur with the previous PVAC, as discussed later. Further, a 20-degree forward tilt was added to the distal circular segment of the new PVAC Gold catheter for a more uniform contact with the PV antrum.

The multiarray septal catheter (MASC™, Medtronic Inc, Minneapolis, MN, USA) is designed to map and ablate the atrial septal wall. It has 12 platinum electrodes on the underside of the array, with fins for added cooling. After the MASC has been introduced through the transseptal puncture site, the electrodes are positioned

Figure 1: The phased RF catheter family and the GeniousTM RF generator. See text for details. (Image courtesy of Medtronic Inc)

PVAC·GOLD   MASC   MAAC   GENius·with·ContactIQ

against the septum by pulling back on the catheter.

The multiarray ablation catheter (MAAC™, Medtronic Inc, Minneapolis, MN, USA) is designed to map and ablate arrhythmogenic drivers in the left atrial (LA) body, such as complex fractionated atrial electrograms (CFAEs). It is composed of 8 finned platinum electrodes affixed to an X-shaped nitinol frame, with 2 electrodes on each arm.

All three catheters monitor electrode-tissue temperature through thermocouples bonded directly to each electrode on the side of the electrode in contact with the tissue. Thermocouples are placed as close as possible to the tissue interface for more accurate temperature monitoring.

A unique feature of the system is the duty-cycled phased RF energy, which is used for lesion formation with all 3 catheters. The GENius™ Multi-Channel RF Ablation Generator (Medtronic, Minneapolis MN, USA) contains 12 independently controlled RF generators for each electrode in the catheter. 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 (Fig. 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 (Fig. 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.[11] 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 (Contact IQ). The bars are yellow if the temperature or the power is too low to cause a lesion, and green when the power and temperature are sufficient for better lesion creation (>3 W and > 50 °C) which has been associated with a better clinical outcome.

Phased RF ablation procedures require a single transseptal puncture and a standard or a stearable transseptal sheath to guide the ablation catheter. Recent recommendations on periprocedural anticoagulation include uninterrupted vitamin K antagonist (VKA) administration for at least 1 month before the procedure and a therapeutic (2-3) INR on the day of the ablation. A heparin iv bolus is administered before or immediately after the transseptal puncture and repeated as required to reach and maintain a target INR level above 350 sec throughout the left atrial access period.

The PVAC or PVAC Gold catheter is used to isolate and then validate the elecrical isolation of all PVs. The catheter is introduced into the sheath with the spiral array extended over a guidewire (0.032 inches in diameter, at least 180 cm in length) through use of a sliding knob on the catheter handle. Passing the valve of the sheath is facilitated by a tube-shaped capture device provided with the catheter. It is recommended to capture the 3-dimensional distal part containing the electrodes under saline in order to eliminate any air bubble possibly trapped within the complex structure of the electrode array. The catheter is advanced through the guiding sheath over the guidewire positioned in one of the PVs. When it enters the LA, the sliding knob is retracted to allow the electrode array to regain its circular shape. Positioning the electrodes at the PV antra is facilitated by the guidewire in the PV being advanced beyond the border of the cardiac silhouette, which also promotes the maintenance of a stable

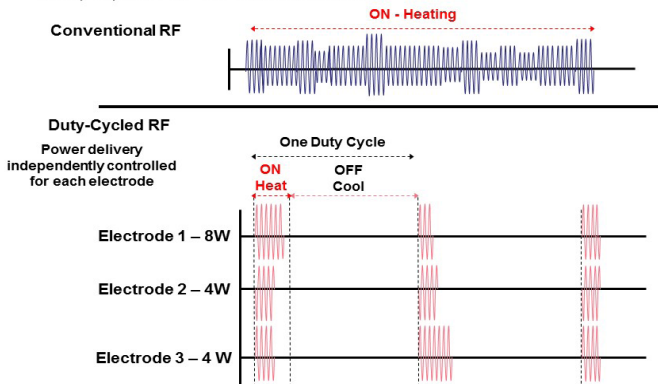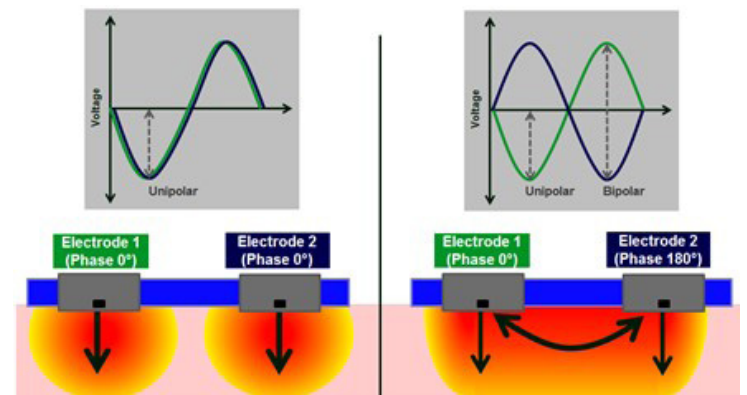## Power Delivery
Duty-Cycled RF vs. Conventional RF

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 neighbouring 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)

position during RF deliveries. PV angiography through the guiding sheath can be used to assess the catheter position in relation to the ostium so as to avoid any RF application inside the PVs. Catheter placement with stable tissue contact on as many electrodes as possible as assessed via the electrogram is preferred. RF energy is applied for 60 sec, usually with a starting bipolar:unipolar ratio of 4:1 or 2:1. It is recommended to switch off any electrode pair that fails to reach at least 50 ℃ during RF delivery in order to in order to avoid ineffective applications due to improper contact at the electrode-tissue interface. Furthermore, when an electrode reaches the target temperature while delivering very low power (1-2 W), it is considered a sign of an undesirably strong electrode-tissue contact or a wedge position of the electrode, and energy delivery to that particular electrode should be switched off.

As electrograms can not be assessed during the delivery of phased RF current because of electrical noise, electrical conduction of the PVs can be assessed between the applications. It is inherent to the electrode design that the intracardiac signals recorded with this circular catheter are smoothed, less detailed and lower in amplitude than those recorded with conventional circular mapping catheters (Fig. 5). Duytschaever reported a 93% overall diagnostic accuracy for the verification of PVI when a conventional mapping catheter was used as a gold standard.[12] Pacing maneuvers or a conventional mapping catheter should be considered whenever doubt remains about PV conduction.[13]

Besides PVI, phased RF ablation of atrial tissue at sites demonstrating CFAEs can be performed through use of the MASC and MAAC devices. The MASC is designed to ablate the septum in response to pulling on the catheter and the transseptal sheath and holding the electrode against the septum. Between RF applications the catheter can be rotated to cover another area of the septum. The MAAC catheter is designed to ablate other sites of the LA, including

the posterior wall.

A significant limitation of current phased RF technology is that due to the many anatomical variations it may be difficult to have a stable tissue contact with these multipolar catheters even after different kinds of maneuvers. Recent data suggest that the inclusion of contact force sensors significantly improves reliability and safety therefore this technology is now considered by many electrophysiologists as the gold standard for left atrial ablation. Phased RF ablation will likely be of greater interest once it has this extra function.

Clinical Results with Phased RF Ablation

Acute Success and Procedural Parameters

Procedural outcomes and follow-up results from some single-center studies are presented in Table 1.[14-24] On the basis of a metaanalysis of 42 publications, Andrade et al.[25] reported an average procedure time of 116.9±33 min and a fluoroscopy time of 26.5±9.6 min with 25.1±3.4 applications per procedure on use of the PVAC only in patients with paroxysmal AF. Procedure and fluoroscopy times for ablations with the PVAC, MASC and MAAC in persistent AF patients were 137.1±29.3 and 31.6±12.4 min, respectively. The data on 1147 patients from 20 studies indicated that acute PVI was achieved with the PVAC alone, without concomitant use of a focal RF ablation catheter, in 98.57% of the patients and in 99.38% of the targeted PVs. It should be noted that mean procedure times below 85 min have been reported from experienced centers for a cohort of paroxysmal[14] or mostly paroxysmal AF patients.[15]

Longer-Term Outcome

Scharf et al. reported results of a survey on 2748 patients treated with phased RF ablation for mostly paroxysmal AF in 20 European centers.[26] In 1669 paroxysmal AF patients, the overall, the first procedure and the AAD-free success rates during a mean follow-up of 11.2 months were 82% 58% and 59% respectively. Similar results were reported from a high-volume center:[22] arrhythmia-free survival after a single procedure without AAD in 120 paroxysmal AF patients was 55% at 1 year and 49% at 2 years. In another analysis by the same group,[21] the PV anatomy did not have a significant effect on the long-term results; only a tendency to a poorer outcome was seen for PVs with diameters > 24 mm.

The Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) trial, a randomized, multicenter study involving 210 patients with persistent AF, compared the effectiveness and safety of phased RF ablation with AAD.[27] All the patients in the ablation group were treated with the PVAC, the MASC and the MAAC. The chronic
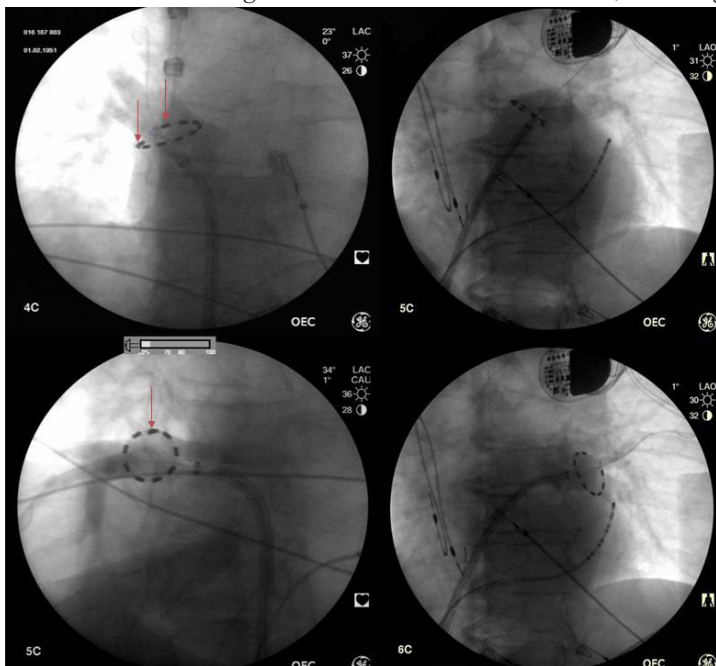
Figure 4: The PVAC and the PVAC Gold positioned in the pulmonary veins. PVAC Gold (9 electrodes) is positioned in the lateral, PVAC (10 platinum electrodes) in the septal pulmonary veins. Note the overlap between poles 1 and 10 of the PVAC in the right inferior vein and a „safe" interelectrode distance in the right superior vein (arrows). See text for explanation
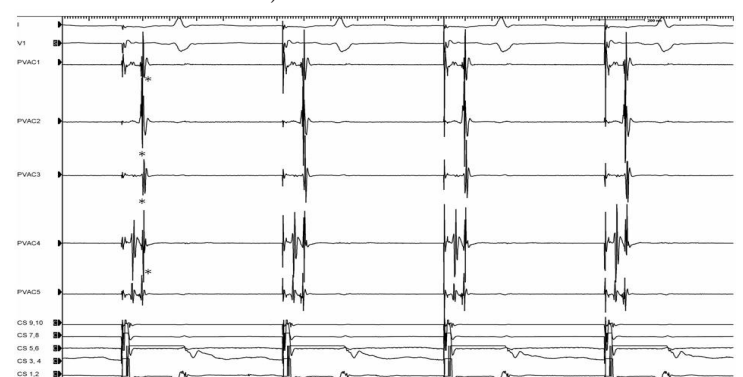
Figure 5: Pulmonary vein potentials recorded by the PVAC from the left superior pulmonary vein during continuous stimulation in the coronary sinus. Pacing artefacts are followed by atrial electrograms and pulmonary vein potentials (*)

Table 1:   **Acute and longer-term results of phased RF ablation**

Study	No.of Pts	Age	Type of AF parox: persistent (%)	Mean Left atrial diameter(mm)	Proc. time (min)	Fluoro time (min)	Additional ablation	Acute success rate (%)	Months of FU	Long term success (%)	
Boersma et al. [14]	98	59±9	100:0	na	84±29	18±9	-	100	6	83	
Fredesrdorf et al.[15]	21	59±12	80:20	na	81±13	30±11	-	99	6	86	
Scharf et al. [16]	50	58±7	long-standing persistent	46±5	155±40	55±35	MASC+MAAC	100	6.3±0.9	70	
Beukema et al.[17]	102	57.9±9.6	90:12	41.2±6.5	139.3±37.72	32.1±11.3	irrigated RF if needed	100	12.2±3.9	60.8	
Wieczorek et al.[18]	88	58±11	100:0	44±4	125±28	21±13	RF	99	>3 and <12 ≥12	82.2	79.2
Duytschaever et al. [19]	77	60±8	100:0	41±4	176±25	na	-	97	3	74	
Wieczorek et al. [20]	73	56±12	100:0	44±3	122±27	20±11	RF if needed	99	6	85	
Mulder et al. [21]	89	59±8	long-standing persistent	42±4	112±32	21±10	MASC+MAAC	100	12	49	
Mulder et al. [22]	120	59	100:0	40±5	86±26	na	-	100	24	49	
Mulder et al. [23]	100	59±9	100:0	40±5	na	na	-	100	12	53	
Nardi et al. [24]	429	60±12	68:32	na	62±15	na	75 patients had 2 procedures	na	22±5	68.5	

effectiveness criterion (defined as the acute isolation of all PVs, a 50 % reduction of CFAE targets, restoration of stable SR at the end of the ablation, and a > 90% reduction in the cumulative atrial arrhythmia (atrial flutter or AF lasting > 10 minutes) time on the 48-hour monitor 6 months postablation as compared with the baseline in the absence of AAD therapy was met in 57.6% of the patients. In the 620 patients treated for persistent/long-standing persistent AF in the European survey.[26] the overall, first procedure and AAD-free success rates at 11.2 months postablation were 70%, 58% and 58%.

The efficacy data of the European survey were also analyzed with respect to the level of experience of the centers reporting the data. Importantly, the overall and first procedure success rates were similar among the higher (79.1% and 68.8%) and lower volume (79.4% and 72.3%) centers. However, a poorer success rate was reported off AAD in the lower- volume centers (49.7%) than in the higher-volume centers (60.8%). Further, the success rates did not either depend on the duration of experience with phased RF ablation or on the number of phased RF procedures performed. Our group reported similar findings:[28] neither the success rate nor the complication rate differed during the 1st, the 2nd and the 3rd 44 patients treated with phased RF ablation at our center.

PVAC Ablation Outcomes in Comparison with Focal RF Ablation

PVAC ablation has been compared with focal RF ablation guided
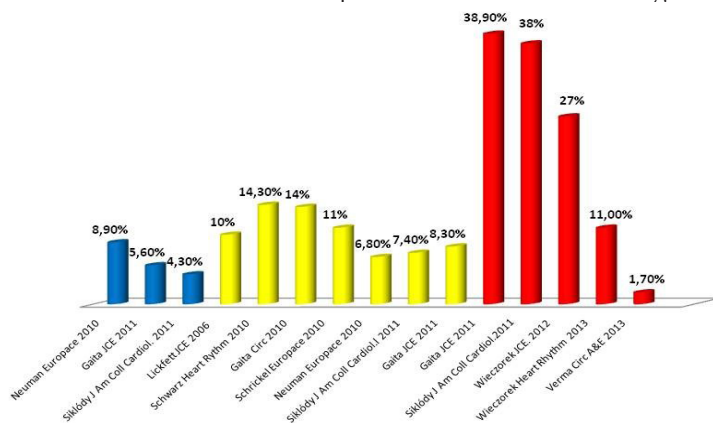

Figure 6:   Incidence of silent cerebral lesions detected by DW MRI in different studies with cryoballoon (blue), irrigated RF (yellow) and phased RF (blue)

by electroanatomical mapping (Table 2) in a number of single-center studies.[29-38] Significantly lower procedure times were consistently reported with phased RF, while the fluoroscopy times were similar or also shorter when the PVAC was used. No difference in efficacy was reported in these trials which involved relatively small numbers of patients and a variable length of follow-up. A comparison of the results of the worldwide survey[39] of procedures in which focal RF ablation was performed in the majority of patients with the data from the European Survey on phased RF ablation[26] likewise suggests a similar outcome with the two techniques. In the first randomized multicenter trial in which PVI with electroanatomically guided wide-area circumferential ablation (WACA; 92 patients) was compared with use of a focal irrigated RF catheter (94 patients), the AF-free survival at 12 months was 56% and 60% respectively.[38] Both the procedure time and the fluoroscopy time were significantly shorter with the PVAC.

A comparison of these 2 technologies as the initial experience with AF ablation in a lower-volume center has also been reported.[30] The first 109 patients undergoing PVI at this center were randomized for 3D mapping-guided focal RF or for phased RF ablation. The 6-month success rate was significantly higher with the PVAC (68%) than with focal ablation (39%), while the complication rates were similar. The procedure and fluoroscopy times were also significantly shorter with phased RF ablation. Although the number of these patients is limited, these data suggest that the influence of operator experience on the clinical success and procedural complications may be less significant during PVI with the PVAC as compared with focal RF ablations.

Complications with Phased RF Ablation

Cerebral Embolization

The risk of cerebral embolization arose as a significant concern relatively early after this technology was introduced in clinical practice. The TTOP-AF[40] study demonstrated a 2.3% acute stroke rate (4/176) in all ablated patients and a per-procedure incidence of 1.7% (4/239). Although the study was published only in 2014, data were presented to the Food and Drug Admininstration in 2011, and the results therefore received publicity earlier. It is noteworthy that strokes occurred within 12 hours postablation on a subtherapeutic INR level in all the patients in the TTOP-AF study suggesting that

Table 2: Phased RF ablation outcomes in comparison with focal RF ablation

Study	No.of Pts	Age	Paroxysmal: Persistent: Long standing AF (%)	Left atrial diameter (mm)	Procedure time (min)	Fluoro time (min)	Acute success rate (%)	Length of FU	Long term success (%)
Bulava et al. [29]	PVAC: 51	56.5±9.9	paroxysmal	41.2±5.4	107±31	16±5	98	202±13 days	77
	RF+ Carto: 51	59.8±11.9		39.7±4.4	208±46	28±8	98.5		71
Choo et al.[30]	PVAC: 38	56.9±10.2	79:2:0	42.0±7.5	168±41	39±14	97	6 months	68
	RF+Carto:	56.2±10.5	60:40:0	40.5±7.5	246±60	73±27	96		40
	47 RF+NavX: 24	62.2±7.7	63:37:0	43.9±6.3	265±60	79±25	100		38
	RF+3D Mapping: 71	58.2±10.2	39:61:0	41.5±7.3	252±60	75±26	97		39
Bittner et al. [31]	PVAC: 40	57±11	53:47:0	43±5	171±40	26±8	99	254±99 days	72
	RF+3D Mapping: 40	59±9	58:42:0	42±7	224±27	35±9	100		68
Khaykin et al. [32]	PVAC: 31	63±10	paroxysmal	39±6	125±25	36±14	na	6 months	67
	RF+3D Mapping: 19	57±12		43±4	135±26	50±16	na		54
Spitzer et al. [33]	PVAC: 388	61.7±9.7	79.9 :17.5: 2.6	42±6	67.0±18.0	15.6±5.7	>99	24months	64.2
	RF+NavX:151	58.1±9.3	54.3 :31.1:14.6	43±5	142.2±35.0	29.3±9.8	>99		48.2
De Greef et al. [34]	PVAC: 79	60±10	66:34:0	41±7	121±41	33±11	100	3 years	65
	RF+Carto: 82	58±10	55:45:0	42±7	169±43	32±15	100		55
Tivig et al.[35]	PVAC: 143	61±10	paroxysmal	40±6	128±38	29±13	na	12months	76
	PVAC: 66	61±10	persistent	46±6	171±39	46±14	na		55
	RF+NavX :155	58.8±10	paroxysmal	40±5	134±43	39±20	na		71
	RF+NavX:56	61±9	persistent	47±7	161±44	44±18	na		52
Looi et al.[36]	PVAC: 75	60±10.1	paroxysmal	48±4.2	135±54	46±29	na	268±176 days	65.3
	RF+Carto: 128	56.3±10.6		44.2±5.6	178±43	48±23	na	266±184 days	65.6
Gal et al.[37]	PVAC:230	56.6±10.3	83.9:16.1 80:20	41.7±4.7	133.9±38.8	31.9±12.3	99.8	43 months	47.7
	RF+Carto: 230	56.1±9.8		40.6±4.9	177.7±48.7	29.7±12.3	99.6		45.5
McReady et al. [38]	PVAC:94	58±12	paroxysmal	38±7	140±43	35±16	98	12months	60
	RF+Carto or NAVx: 94	62±11		39±5	167±42	42±20	97		56

not necessarily the ablation technology per se, but rather inadequate anticoagulation may possibly have contributed to these cerebral events. The results of the recently published COMPARE[40] trial underscores the critical importance of periprocedural anticoagulation: point-by-point RF antrum isolation with or without CFAE ablation was associated with a symptomatic periprocedural thromboembolic event rate of 4.9% when warfarin was discontinued with heparinbridging as compared with a 0.33% event rate on uninterrupted warfarin therapy. The majority of thromboembolic events occurred in non-paroxysmal AF patients. Following the completion of the TTOP-AF study, more favorable safety results were published by a center with extensive experience in phased RF ablation: 2 strokes and 5 transient ischemic attacks (TIAs) occurred during 662 procedures (with use of the PVAC alone in the majority of procedures) in patients with paroxysmal and persistent AF.[22] Cerebral ischemic events also occurred within 24 hours postablation in this study in 6 of the 7 patients, the INR during the procedure was <2.0 in 3 of them. In the European survey on phased RF ablation in 2748 patients, a total stroke and TIA incedence of 1,1% was reported.[26] In a metaanalysis of 42 papers which included the data on 1162 patients treated for paroxysmal and 347 patients with persistent AF, the incidence of thromboembolic complications was 0.63%, including 6 strokes, 2 TIAs and 2 myocardial infarctions.[25] In the prospective multicenter trial in which electroanatomically guided WACA was compared with PVAC ablation, 2 strokes (2%) occurred in the latter group, both within 48 hours after the ablation, with heparin-bridging strategy applied in both.[38]

Besides clinically manifest strokes, AF ablation might also result in a clinically silent cerebral embolism. Silent cerebral ischemia (SCI) can be detected by diffusion-weighted (DW) magnetic resonance imaging (MRI) after the ablation procedure.[41-46] The SCIs frequently appear at multiple locations which are not related to a certain vascular territory but represent different vascular distributions, suggesting the embolic nature of these lesions. The reported rate of postablation SCIs is highly variable, ranging from 1.7% (11) to 38.9%. In the earlier publications, a significant correlation was demonstrated between the incidence of these lesions and the ablation technology, with phased RF ablation consistently posing the highest risk. Siklódy et al. reported
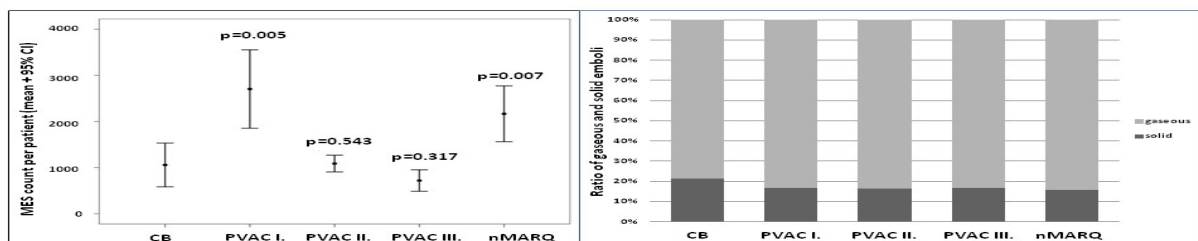

Figure 7: Cerabral microembolization during pulmonary vein isolation with different ablation technologies. Left: A plot of the mean number of microembolic signals (MES) recorded by transcranial Doppler (TCD) in the middle cerebral artery in each treatment group as compared with the cryoballoon (CB) group. Besides CB and nMARQ, a novel circular multipolar irrigated RF technology, 3 different phased RF methods were compared with respect to cerebral microembolization: phased RF with the older ablation generator (PVAC I), phased RF with avoiding distal PVAC poles to come in close proximity (PVAC II) and phased RF with newer software generation which contains a special contact detection algorithm to avoid tissue overheating in improper contact scenarios and do not permit simultaneous use of distal PVAC electrodes (PVAC III). Right: Mostly gaseous microemboli were detected with different technologies. (Kiss et al [58]; reproduced with permission).

an SCI incidence of 33% in 24 AF patients after ablation with the PVAC, as compared with 7.4% and 4.3% in those ablated with focal irrigated RF and the CB technology, respectively.[44] Similarly, Gaita et al. found a significantly higher SCI rate after PVAC ablation (38.9%) as compared with irrigated RF or CB (8.3% and 5.6% respectively)[45] Although 2/3 of the lesions were at most 3 mm in diameter and the majority, (especially the smaller ones) disappeared within days or weeks after ablation,[47] the phenomenon generated significant concern as regards the potential long-term consequences on the cognitive function of these patients.[48-49] In line with the MRI results, intraoperative transcranial Doppler (TCD) detection of cerebral microembolization also indicated a technology-related difference: our group recorded a significantly higher number of mostly gaseous microembolic signals (MESs) during PVI with the PVAC than with CB.[50] It may be noted that the majority of MESs were associated with the energy delivery phase of PVAC ablations, while a relatively even distribution was demonstrated during CB ablation.

Lower SCI rates have been reported with the phased RF technology in more recent publications,[51-52] and a cerebral lesion was demonstrated in only 1 of 60 patients in the ERACE multicenter trial, which enrolled patients with paroxysmal AF who underwent PVI with the PVAC.[53] The significant reduction achieved in clinically silent microembolization as demonstrated by these DW MRI studies might be attributed to the strict periprocedural anticoagulation, including the use of uninterrupted VKA before the procedure and heparin administration to reach an ACT target > 350 sec during ablation. Further, on the basis of the preclinical data, refinements in specific technical elements of the phased RF ablation have been implemented. In an animal model, Haines observed significantly enhanced microembolization with blended unipolar:bipolar energy delivered through PVAC electrodes in close proximity to each other, which was a likely common scenario, thanks to the squeezed position of the distal PVAC loop.[54-55] While actual physical contact between any two electrodes results in an electrical short circuit and the termination of RF delivery, a reduced interelectrode distance (less than the fixed 3 mm between two neighboring electrodes mounted on the distal circular segment of the PVAC) without contact may lead to blood and tissue overheating, due to a high current density during the RF delivery. Simple measures to avoid this possibility include a careful fluoroscopic assessment of the electrode positions, exclusion of simultaneous RF delivery to electrodes 1 and 10, and a software modification implemented in the GENius generator, which supports simultaneous RF delivery to a maximum of 9 electrodes. In keeping with this concept, the number of electrodes on the new PVAC Gold catheter is limited to 9. Animal data also pointed to a tendency for more microemboli with more bipolar RF delivery. It is therefore reasonable to change the earlier practice of starting the energy delivery in 4:1 bipolar:unipolar mode at each PV, and begin with a 2:1 ratio, the current practice in most centers. The animal model also revealed that the introduction of air into the LA via the transseptal sheath potential was a potential source of gaseous emboli. A significantly larger air volume was measured during the introduction of the PVAC, possibly because of its more complex shape as compared with that of a conventional focal RF catheter. To prevent air entrapment, submerged capture of the electrode array in a saline bath prior to insertion into the FlexCath sheath is recommended.

Besides the procedural changes described above, the GENius RF generator has also been modified in recent years. An improved energy titration algorithm was implemented 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, thereby avoiding high temperature peaks. The importance of the catheter-tissue contact has been stressed since the introduction of contact force measurement for focal RF ablation catheters.[56] With multipolar ablation, this becomes even more critical, as the maintenance of good contact simultaneously on multiple electrodes can be challenging, and the possibility of direct contact force measurement with this technology is not yet available. This concept is supported by our previous study: an analysis of temperature and power data obtained at high-resolution sampling from the GENius generator demostrated increased microembolus formation during intermittent contact scenarios when low temperature was compensated by increased power, which resulted in a temperature overshoot when the contact was re-established.[57] Further, in the most recent issue of the GENius software, RF delivery is limited to 9 electrodes, thereby providing a definite solution regarding the problem of E1-E10 interaction.

Similarly to the trend observed in recent DW MRI studies on the rate of new SCI lesions after phased RF ablation, our group observed a significant decrease in the number of cerebral MESs detected by TCD.[58] A Comparison of cerebral microembolization during PVAC ablations before and after the procedural changes discussed above were implemented at our center revealed a significant decrease to the level obtained with a CB (Fig. 6). The significant reduction in microembolization with phased RF was clearly related to the elimination of the MESs during the energy delivery period of the procedure. It is noteworthy that the MESs were largely gaseous in nature in all the treatment groups.

Other Complications

Other potential complications during phased RF ablation are similar to what may occur during left atrial ablation with any other technology and include problems at vascular access sites, pericardial tamponade and PV stenosis.

In the meta-analysis by Andrade et al., 3 pericardial tamponades and 3 effusions were reported in 1719 patients; 1 out of 931 patients exhibited symptomatic PV stenosis.[25] A higher incidence of PV stenosis at long-term follow-up emerged in a recent study.[59] A 25-50%-degree stenosis was found in 37%, one of 50-70 % in 9% and one of > 70% in 3% of the patients. However, these mostly mild-to-moderate narrowings resulted in no symptoms and ventilation/scans demonstrated no abnormalities. Clinically relevant injury to the esophagus, one of the most feared complications of AF ablation with high mortality and phrenic nerve palsy, has never been reported with phased RF ablation.

Ongoing Trials with Phased RF Ablation

The PRECISION GOLD Study is a prospective multi-center trial, the main objective of which is to evaluate the incidence of asymptomatic cerebral lesions after PVI using the new PVAC Gold for PVI in patients with paroxysmal AF. The trial was completed last year and full-length publication is expected during 2015.

The ongoing VICTORY AF (ClinicalTrials.gov Identifier: NCT01693120) is a prospective global, multi-center, single-arm, controlled, unblinded, investigational clinical study, with the purpose of evaluating the risks of procedure and/or device-related strokes

in subjects with persistent or long-standing persistent atrial AF undergoing ablation with the Phased RF System. Patient enrollment in US and European centers has already started.

Conclusion

Phased RF ablation involves the use of anatomically designed, multi-electrode catheters with tissue temperature monitoring and a closed-loop power control generator to create contiguous lesions in a simpler procedure as compared with conventional AF ablation. The majority of the literature data relate to PVI with the PVAC in patients with paroxysmal AF. Similar acute and longer-term success rates, but significantly lower procedure and fluoroscopy times with PVAC ablation have consistently been reported relative to other AF ablation methods. The incidence of manifest and silent cerebral complications has fallen significantly in recent reports, thanks to important changes in the periprocedural anticoagulation regime, procedural modifications and improvements in software regulations of the RF generator. Evaluation of the new PVAC Gold catheter is currently in progress. Data from some studies suggest a short learning curve and favorable results with this technology, even in lower-volume centers and in the hands of operators with limited experience in AF ablation. The safety and efficacy outcomes of phased RF ablation, including mapping and ablation of arrhythmogenic drivers in the LA, body in addition to PVI in patients with persistent AF are currently being evaluated in the ongoing VICTORY AF trial.

References

1. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 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. Europace 2012; 14: 528-606.

2. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010; 303: 333-340.

3. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. European Heart Journal 2012; 33: 2719-2747.

4. Rolf S, Hindricks G, Sommer P, Richter S, Arya A, Bollmann A, Kosiuk J, Koutalas E. Electroanatomical mapping of atrial fibrillation: Review of the current techniques and advances. J Atrial Fibrillation 2015; 7: 57-68.

5. Van Belle Y, Janse P, Rivero-Ayerza MJ, Thornton AS, Jessurun ER, Theuns D, Jordaens L.Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome. Eur Heart J 2007; 28: 2231-2237.

6. Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, Kurzidim K, Berkowitsch A, Koller M, Heintze J, Scholz U, Wetzel U, Schneider MA, Horstkotte D, Hamm CW, Pitschner HF. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol 2008; 52: 273-278.

7. Dukkipati SR, Kuck KH, Neuzil P, Woollett I, Kautzner J, McElderry HT, Schmidt B, Gerstenfeld EP, Doshi SK, Horton R, Metzner A, d'Avila A, Ruskin JN, Natale A, Reddy VY. Pulmonary vein isolation using a visually guided laser balloon catheter: the first 200-patient multicenter clinical experience. Circ Arrhythm Electrophysiol. 2013; 6: 467–472.

8. Sohara H, Satake S,Takeda H, Yamaguch Y, Toyama H, Kumagai K, Kuwahara T, Takahashi A, Ohe T. Radiofrequency hot balloon catheter ablation for the treatment of atrial fibrillation: A 3-center study in Japan. J Arrhyth 2013; 29: 20-27.

9. Metzner A, Chun KR, NevenK,Fuernkranz A, Quyang F, Antz M,Tilz R, Zerm T, Koektuerk B, Wissner E, Koester I, Ernst S, Boczor S, Kuck KH, Schmidt B. Long-term clinical outcome following pulmonary vein isolation with high-intensity focused ultrasoun balloon catheters in patients with paroxysmal atrial fibrillation. Europace 2010; 12: 188-193.

10. Boersma L, Duytschaever M, Geller JC, Scarf C. The PVAC Workbook. London, UK: Remedica; 2010:1-21, 41-67.

11. Wijffels MC, Van Oosterhout M, Boersma LV, Werneth R, Kunis C, Hu B, Beekman JD, Vos MA. Characterization of In Vitro and In Vivo Lesions Made by a Novel Multichannel Ablation Generator and a Circumlinear Decapolar Ablation Catheter. J Cardiovasc Electrophysiol. 2009; 20: 1142-1148.

12. Duytschaever M, Anne W, Papiashvili G, Vandekerckhove Y, Tavernier R. Mapping and isolation of the pulmonary veins using the PVAC catheter. Pacing Clin Electrophysiol 2010; 33: 168-178.

13. von Bary C, Fredersdorf-Hahn S, Heinicke N, Jungbauer C, Schmid P, Riegger GA, Weber S. Comparison of PV signal quality using a novel circular mapping and ablation catheter versus a standard circular mapping catheter. J Interv Card Electrophysiol 2011; 31: 131-139.

14. Boersma LV, Wijffels MC, Oral H, Wever EF, Morady F. Pulmonary vein isolation by duty-cycled bipolar and unipolar radiofrequency energy with a multielectrode ablation catheter. HeartRhythm 2008; 5: 1635-1642.

15. Fredersdorf S, Weber S, Jilek C, Heinicke N, VON Bary C, Jungbauer C, Riegger GA, Hamer OW, Jeron A. Safe and rapid isolation of pulmonary veins using a novel circular ablation catheter and duty-cycled RF generator. J Cardiovasc Electrophysiol 2009; 20: 1097-1101.

16. Scharf C, Boersma L, Davies W, Kanagaratnam P, Peters NS, Paul V, Rowland E, Grace A, Fynn S, Dang L, Oral H, Morady F. Ablation of persistent atrial fibrillation using multielectrode catheters and duty-cycled radiofrequency energy. J Am Coll Cardiol. 2009; 54: 1450-1456.

17. Beukema RP, Beukema WP, Smit JJ, Ramdat Misier AR, Delnoij PP, Wellens H, Elvan A. Efficacy of multi-electrode duty-cycled radiofrequency ablation for pulmonary vein disconnection in patients with paroxysmal and persistent atrial fibrillation. Europace 2010; 12:502-507.

18. Wieczorek M, Hoeltgen R, Brueck M, Bandorski D, Akin E, Salili AR. Pulmonary vein isolation by duty-cycled bipolar and unipolar antrum ablation using a novel multielectrode ablation catheter system: first clinical results. J Interv Card Electrophysiol 2010; 27: 23-31.

19. Duytschaever M, Anne W, Papiashvili G, Vandekerckhove Y, Tavernier R. Mapping and isolation of the pulmonary veins using the PVAC catheter. Pacing Clin Electrophysiol 2010; 33: 168-178.

20. Wieczorek M, Hoeltgen R, Brueck M, Bandorski D, Akin E, Salili AR. Pulmonary vein isolation by duty-cycled bipolar and unipolar antrum ablation using a novel multielectrode ablation catheter system: first clinical results. J Interv Card Electrophysiol 2010; 27: 23-31.

21. Mulder AA, Wijffels MC, Wever EF, Boersma LV. Pulmonary vein isolation and left atrial complex-fractionated atrial electrograms ablation for persistent atrial fibrillation with phased radio frequency energy and multi-electrode catheters: efficacy and safety during 12 months follow-up. Europace 2011; 13:1695-1702.

22. Mulder AA, Balt JC, Wijffels MC, Wever EF, Boersma LV. Safety of pulmonary

vein isolation and left atrial complex fractionated atrial electrograms ablation for atrial fibrillation with phased radiofrequency energy and multi-electrode catheters. Europace 2012; 14: 1433-1440.

23. Mulder AA, Wijffels MC, Wever EF, Boersma LV. Early recurrence of atrial fibrillation as a predictor for 1-year efficacy after successful phased RF pulmonary vein isolation: evaluation of complaints and multiple Holter recordings. Int J Cardiol 2013; 16: 56-60.

24. Nardi S, Argenziano L, Cappato R, de Martino G, Esposito C, Scaglione M, Borrello F, Maglia G. Ablation of paroxysmal and persistent atrial fibrillation with multielectrode phased radiofrequency duty-cycled catheters: long-term results from a large cohort of patients. J Cardiovasc Med. 2013; 14: 879-885.

25. Andrade JG, Dubuc M, Rivard L, Guerra PG, Mondesert B, Macle L, Thibault B, Talajic M, Roy D, Khairy P. Efficacy and safety of atrial fibrillation ablation with phased radiofrequency energy and multielectrode catheters. Heart Rhythm. 2012; 9: 289-296.

26. Scharf D, Ng GA, Wieczorek M, Deneke T, Furniss SS, Murray S, Debruyne P, Hobson N, Berntsen RF, Schneider MA, Hauer HA, Halimi F, Boveda S, Asbach S, Boesche L, Zimmermann M, Brigadeau F, Taieb J, Merkel M, Pfyffer M, Brunner-La Rocca HP, Boersma LV. European survey on efficacy and safety of duty-cycled radiofrequency ablation for atrial fibrillation. Europace. 2012; 14: 1700-1707.

27. Hummel J, Michaud G, Hoyt R, DeLurgio D, Rasekh A, Kusumoto F, Giudici M, Dan D, Tschopp D, Calkins H, Boersma L; TTOP-AF Investigators. Phased RF ablation in persistent atrial fibrillation. Heart Rhythm 2014; 11: 202-209.

28. Martirosyan M, Kiss A, Nagy-Baló E, Sándorfi G, Tint D, Edes I, Csanádi Z. Learning curve in circular multipolar phased radiofrequency ablation of atrial fibrillation. Cardiol J 2014; [Epub ahead of print]

29. Bulava A, Haniš J, Sitek D, Ošmera O, Karpianus D, Snorek M, Rehoušková K, Toušek F, Pešl L. Catheter ablation for paroxysmal atrial fibrillation: a randomized comparison between multielectrode catheter and point-by-point ablation. Pacing Clin Electrophysiol 2010; 33:1039-1046.

30. Choo WK, Farwell D, Harris S. Experience of atrial fibrillation ablation in a new cardiac centre using three-dimensional mapping and multielectrode duty-cycled radiofrequency ablation. Arch Cardiovasc Dis 2011; 104:396-402.

31. Bittner A, Mönnig G, Zellerhoff S, Pott C, Köbe J, Dechering D, Milberg P, Wasmer K, Eckardt L. Randomized study comparing duty-cycled bipolar and unipolar radiofrequency with point-by-point ablation in pulmonary vein isolation. Heart Rhythm 2011; 8: 1383-1390.

32. Khaykin Y, Zarnett L, Friedlander D, Wulffhart ZA, Whaley B, Giewercer D, Tsang B, Verma A. Point-by-point pulmonary vein antrum isolation guided by intracardiac echocardiography and 3D mapping and duty-cycled multipolar AF ablation: effect of multipolar ablation on procedure duration and fluoroscopy time. J Interv Card Electrophysiol 2012; 34: 303-310.

33. Spitzer SG, Karolyi L, Weinmann T, Scharfe F, Rämmler C, Otto T, Jung F, Kadalie CT. Multielectrode phased radiofrequency ablation compared with point-by-point ablation for pulmonary vein isolation – outcomes in 539 patients. Research Reports in Clinical Cardiology; 2014, Vol. 5, p11

34. De Greef Y, Buysschaert I, Schwagten B, Stockman D, Tavernier R, Duytschaever M. Duty-cycled multi-electrode radiofrequency vs. conventional irrigated point-by-point radiofrequency ablation for recurrent atrial fibrillation: comparative 3-year data. Europace 2014; 16: 820-825.

35. Tivig C, Dang L, Brunner-La Rocca HP, Özcan S, Duru F, Scharf C. Duty-cycled unipolar/bipolar versus conventional radiofrequency ablation in paroxysmal and persistent atrial fibrillation. Int J Cardiol. 2012; 157:185-191.

36. Looi KL, Gajendragadkar P, Taha T, Elsik M, Scully E, Heck P, Fynn S, Virdee M, Begley D. Long-term outcomes (>2 years) of atrial fibrillation ablation using a multi-electrode ablation catheter in patients with paroxysmal atrial fibrillation. J Interv Card Electrophysiol 2013; 36: 61-69.

37. Gal P, Aarntzen AE, Smit JJ, Adiyaman A, Misier AR, Delnoy PP, Elvan A. Conventional radiofrequency catheter ablation compared to multi-electrode ablation for atrial fibrillation. Int J Cardiol. 2014; 176: 891-895.

38. McCready J, Chow AW, Lowe MD, Segal OR, Ahsan S, de Bono J, Dhaliwal M, Mfuko C, Ng A, Rowland ER, Bradley RJ, Paisey J, Roberts P,Morgan JM, Sandilands A, Yue A, Lambiase PD. Safety and efficacy of multipolar pulmonary vein ablation catheter vs. irrigated radiofrequency ablation for paroxysmal atrial fibrillation: a randomized multicentre trial. Europace. 2014; 16: 1145-1153

39. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010; 3: 32-38.

40. Di Biase L, Gaita F, Toso E, Santangeli P, Mohanty P, Rutledge N, Yan X, Mohanty S, Trivedi C, Bai R, Price J, Horton R, Gallinghouse GJ, Beheiry S, Zagrodzky J, Canby R, Leclercq JF, Halimi F, Scaglione M, Cesarani F, Faletti R, Sanchez J, Burkhardt JD, Natale A. Does periprocedural anticoagulation management of atrial fibrillation affect the prevalence of silent thromboembolic lesion detected by diffusion cerebral magnetic resonance imaging in patients undergoing radiofrequency atrial fibrillation ablation with open irrigated catheters? Results from a prospective multicenter study. Heart Rhythm. 2014; 11: 791-798.

41. Lickfett L, Hackenbroch M, Lewalter T, Selbach S, Schwab JO, Yang A, Balta O, Schrickel J, Bitzen A, Luderitz B, Sommer T. Cerebral diffusion-weighted magnetic resonance imaging: A tool to monitor the thrombogenicity of left atrial catheter ablation. J Cardiovasc Electrophysiol. 2006; 17: 1-7.

42. Schrickel JW, Lickfett L, Lewalter T, Mittman-Braun E, Selbach S, Strach K, Nahle CP, Schwab JO, Linhart M, Andrie R, Nickenig G, Sommer T. Incidence and predictors of silent cerebral embolism during pulmonary vein catheter ablation for atrial fibrillation. Europace. 2010; 12: 52-57.

43. Gaita F, Caponi D, Pianelli M, Scaglione M, Toso E, Cesarani F, Boffano C, Gandini G, Valentini MC, De Ponti R, Halimi F, Leclercq JF. 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; 122: 1667-1673.

44. Siklódy C. H., T. Deneke, M. Hocini, H. Lehrmann, D.I. Shin, S. Miyazaki, S. Henschke, D. Kalusche, M. Haissague, T. Arentz. Incidence of asymptomatic embolic events following pulmonary vein isolation procedures: comparison between different ablation devices. J Am Coll Cardiol. 2011; 58: 681-688.

45. Gaita F, Leclercq JF, Schumacher B, Scaglione M, Toso E, Halimi F, Schade A, Froehner S, Ziegler V, Sergi D, Cesarani F, Blandino A. 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 Cardiovascular Electrophysiol. 2011; 22: 961-968.

46. Neumann T, Kuniss M, Conradi G, Janin S, Berkowitsch A, Wojcik M, Rixe J, Erkapic D, Zaltsberg S, Rolf A, Bachmann G, Dill T, Hamm CW, Pitschner HF. Medafi-trial (micro-embolization during ablation of atrial fibrillation): Comparison of pulmonary vein isolation using cryoballoon technique vs. radiofrequency energy. Europace. 2011; 13: 37-44.

47. Deneke T, Shin DI, Balta O, Bünz K, Fassbender F, Mügge A, Anders H, Horlitz M, Päsler M, Karthikapallil S, Arentz T, Beyer D, Bansmann M. Postablation asymptomatic cerebral lesions: long-term follow up using magnetic resonance imaging. Heart Rhythm. 2011; 8: 1705-1711.

48. Schwarz N, Kuniss M, Nedelmann M, Kaps M, Bachmann G, Neumann T, Pitschner HF, Gerriets T. Neuropsychological decline after catheter ablation of atrial fibrillation. Heart Rhythm. 2010; 7: 1761-1767.

49. Medi C, Evered L, Silbert B, et al. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. J Am Coll Cardiol 2013; 62: 531-539.

50. Nagy-Baló E, Tint D, Clemens M, Beke I, Kovács RK, Csiba L, Édes I, Csanádi Z. Transcranial Measurement Of Cerebral Microembolic Signals During Pulmonary

Vein Isolation: A Comparison Of Two Ablation Techniques. Circ Arrhythm Electrophysiol.2013; 6: 473-480.

51. Wieczorek 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; 10: 953-959.

52. Wieczorek M, Lukat M, Hoeltgen R, Condie C, Hilje T, Missler U, Hirsch J, Scharf C. Investigation into causes of abnormal cerebral MRI findings following PVAC duty-cycled, phased RF ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2013; 24: 121-128.

53. Verma A, Debruyne P, Nardi S, Deneke T, DeGreef Y, Spitzer S, Balzer JO, Boersma L; ERACE Investigators. Evaluation and reduction of asymptomatic cerebral embolism in ablation of atrial fibrillation, but high prevalence of chronic silent infarction: Results of the ERACE trial. Circ Arrhythm Electrophysiol. 2013; 6: 835-842.

54. 5Haines 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; 6: 16-22

55. 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; 6: 23-30.

56. 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; 6: 327-333.

57. Nagy-Balo E, Kiss A, Condie C, Stewart M, Edes I, Csanadi Z. Predictors of cerebral microembolization during phased radiofrequency ablation of atrial fibrillation: Analysis of biophysical parameters from the ablation generator. Heart Rhythm 2014; 11: 977-983.

58. Kiss A, Nagy-Baló E, Sándorfi G, Edes I, Csanádi Z. Cerebral microembolization during atrial fibrillation ablation: Comparison of different single-shot ablation techniques. Int J Cardiol 2014; 174: 276-281.

59. Compier MG, Leong DP, Marsan NA, Delgado V, Zeppenfeld K, Schalij MJ, Trines SA. Duty-cycled bipolar/unipolar radiofrequency ablation for symptomatic atrial fibrillation induces significant pulmonary vein narrowing at long-term follow-up. Europace. 2013; 15: 690-696.