What Is the Acute Antral Lesion Size After Pulmonary Vein Isolation Using Different Balloon Ablation Technologies?

Laura Perrotta, MD; Athanasios Konstantinou, MD; Stefano Bordignon, MD;
Alexander Fuernkranz, MD; Daniela Dugo, MD; KR Julian Chun, MD; Boris Schmidt, MD

Background: Clinical outcome after pulmonary vein isolation (PVI) may be linked to both durability of PVI and the antral lesion size. Data on balloon-guided technologies are scarce. We investigated the size of the isolated surface area (ISA) acutely after PVI achieved by cryoballoon (CB) or laser balloon (LB), both using voltage mapping.

Methods and Results: In 40 patients (73% male, mean age 66 ± 9 years), a bipolar voltage map before and after PVI in sinus rhythm was acquired to delineate the isolated antral surface area (IASA, contiguous area of low voltage <0.5 mV) and the ISA (relative size of the low-voltage area in relation to the whole antral surface area including the posterior wall). IASA (CB: 57 ± 14 cm² vs. LB: 42 ± 15 cm²; $P=0.002$) as well as ISA ($65 \pm 8\%$ vs. $54 \pm 10\%$; $P=0.001$) were significantly larger in the CB than in the LB group. No periprocedural complications occurred. During a mean follow-up of 326 ± 142 days, 4/20 and 5/20 patients experienced an AF/AT recurrence in the CB and LB groups, respectively. No differences in clinical outcome were observed between patients with a large ($\geq 55\%$) or small ($<55\%$) ISA.

Conclusions: Balloon-guided PVI is associated with antral lesion formation. CB-guided PVI is associated with the largest ISA as compared with LB procedures. ISA size did not correlate with clinical outcome after a single procedure in the present study population.

Key Words: Ablation; Atrial fibrillation; Scarring; Voltage mapping

Electrical pulmonary vein isolation (PVI) is the cornerstone of any ablation procedure for patients with paroxysmal atrial fibrillation (PAF).^{1,2} Patients' clinical outcomes are predominantly determined by the durability of electrical PVI.^{3–5} Aside from triggered activity emanating from the myocardial PV sleeves, the complex peri-ostial atrial myocardium is deemed to contribute to the initiation and perpetuation of AF.⁶ Moreover, the antral region houses numerous ganglionated plexi and rotors potentially sustaining AF.^{7–10} Nonetheless, controversy exists on the value of encircling the peri-ostial tissue by wide antral circumferential ablation lines as opposed to a more distal (so-called segmental) ablation approach.^{11,12} A recent study found a correlation between the area of isolated peri-ostial myocardium and clinical outcome in patients treated with irrigated radiofrequency current (RF) ablation.¹³ Although novel ablation devices such as the cryoballoon (CB; Arctic Front Advance™, Medtronic) and the laser balloon (LB; HeartLight™, CardioFocus) have shown favorable rates of acute and durable PVI, data on the area of isolated atrial antral myocardium following a balloon-based PVI approach are scarce.^{14–16} We therefore investigated the size of the isolated antral surface area (IASA)

as well as the isolated surface area (ISA; relative size of the low-voltage area (LVA) in relation to the whole antral surface area including the posterior wall) acutely after PVI achieved by balloon ablation devices using voltage mapping.

Methods

Patients aged 18–80 years with symptomatic drug-refractory paroxysmal or short-lasting persistent (<6 months episode duration) AF indicated for PVI were eligible for this study. Prior to enrolment patient informed consent was obtained. The institutional review board approved the study.

Patients were excluded if they had undergone a previous PVI attempt or had a left atrial (LA) size >55 mm, valvular dysfunction $>II$, or a LVA prior to PVI detected by bipolar voltage mapping (see below).

Baseline Assessment

Transthoracic and transesophageal echocardiography was performed before the procedure in each patient in order to assess LA size, valve patency and to rule out LA thrombus.

Received April 11, 2016; revised manuscript received October 20, 2016; accepted November 16, 2016; released online December 14, 2016 Time for primary review: 11 days

Cardio-angiological Center Bethanien, Markus Hospital, Frankfurt/M., Germany

Mailing address: Boris Schmidt, MD, FHRS, Cardioangiologisches Centrum Bethanien, Wilhelm Epstein-Str. 4, 60431 Frankfurt/M.; Germany. E-mail: b.schmidt@ccb.de

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Figure 1. Post-ablation voltage measurements. (**Left**) Post-ablation voltage map displayed in a color-coded fashion (grey: ≤ 0.5 mV; purple ≥ 1.0 mV). The level of ablation scar was quantitatively assessed by measuring post-ablation low-voltage areas (in grey). As a first step, each PV ostium was defined (black lines around each PV: RSPV, RIPV, LSPV, LIPV); next, the left and right isolated antral surface areas (IASA-L and IASA-R) were manually measured as low-voltage areas (in grey) around the ipsilateral PV ostia (**Right**). As a sum, the total IASA ($\text{IASA-T} = \text{IASA-L} + \text{IASA-R}$) was calculated. The non-ablated LA posterior wall area (LA PW) is the purple area between the posterior border of the low-voltage post-ablation areas and was determined by drawing horizontal lines between the most cranial and most caudal points of the low-voltage area around the PV ostia, respectively (**Left & Right**). LAA, left atrial appendage; RSPV, right superior pulmonary vein.

Electrophysiological Procedure

The procedures were performed under deep sedation, using boluses of midazolam and fentanyl, as well as continuous infusion of propofol 1%. Throughout the procedure non-invasive blood pressure and oxygen saturation were continuously monitored. An esophageal temperature probe (SensiTherm™, St. Jude Medical, MN, USA) was inserted trans-orally to monitor esophageal temperature during ablation (cutoff temperature for CB 15°C and for LB or RF 39°C).

After placing 2 multipolar catheters in the coronary sinus and at the His bundle, a single transeptal puncture was performed using the modified Brockenbrough technique. An 8.5F sheath (SL1; St. Jude Medical) was advanced into the LA. Prior to transeptal puncture unfractionated heparin was administered to maintain activated clotting time between 300 and 350 s. Selective PV angiography was performed to identify the PV ostia. A circular mapping catheter (CMC; Biosense Webster Inc., CA, USA) was placed at the PV ostium to record PV potentials through a computerized EP-system (Axiom Sensis XP, Siemens, Germany) and was then used as a roving catheter to reconstruct the LA anatomy and the baseline voltage map.

Thereafter, the single transeptal sheath was exchanged for a 12F steerable sheath.

Ablation Protocols

CB-Guided PVI In the CB group, the “single big balloon strategy” was pursued.¹⁷ A 2nd-generation 28-mm balloon (Arctic Front Advance™, Medtronic) was introduced into the LA via the 12F steerable sheath (FlexCath™, Medtronic). Mapping of the PV was performed before, during and after freezing with an endoluminal spiral mapping catheter (Achieve™, Medtronic). Occlusion angiograms were used to obtain optimal PV occlusion and an ostial/antral balloon position. Cryothermal energy was deployed for 240 s at each PV followed by one “bonus” application (240 s) after successful PVI.¹⁸

LB-Guided PVI In the LB group, the sizeable balloon (HeartLight™, CardioFocus, MA, USA) was navigated to the individual PV by the steerable sheath and inflated to obtain optimal PV occlusion. Ablation lesions were deployed in a contiguous fashion under visual guidance, titrating the energy from 5.5 to 12 W (20–30 s ablation time) according to the degree of tissue exposure.

After complete visually guided circular ablation, the PVs were remapped for entrance block using the CMC. In the case of ambiguous PV recordings, differential pacing and pacing from the CMC was performed to verify PVI. In the case of residual LA-to-PV conduction, additional ablation was carried out using the LB according to the activation sequence in the CMC as recently described.¹⁹

During ablation at the right superior pulmonary vein (RSPV), diaphragmatic function was monitored by continuous pacing (12 V, 2.9 ms) of the right phrenic nerve with a 6F diagnostic catheter positioned in the superior vena cava in both balloon groups. If loss or weakening of capture was observed, energy delivery was instantly terminated.

LA Voltage Mapping A bipolar voltage map using NavX Ensite Velocity™ (St. Jude Medical) before and after PVI in sinus rhythm was acquired. An octapolar catheter was placed in the coronary sinus to obtain a stable reference. LA geometry and peak-to-peak voltages were collected using the decapolar CMC (15 mm, with 2–5–2-mm inter-electrode spacing) as a roving catheter. The bipolar electrograms were filtered with a highpass of 30 Hz and a lowpass of 300 Hz. High-density mapping was performed along the PV ostia. After map completion, all acquired points were reassessed and manually edited offline according to predefined criteria: elimination of atrial premature beats, artifacts and far-field EGMs (Electrograms) of the LA appendage. LVAs were defined as contiguous areas of bipolar voltage amplitude ≤ 0.5 mV.²⁰ Maps were automatically displayed in a color-coded fashion (grey: ≤ 0.5 mV; purple ≥ 1.0 mV). If LVAs were detected before ablation, the

Table 1. Baseline Characteristics of the Study Population of Patients With AF

	All (n=40)	LB (n=20)	CB (n=20)	P value
Age (years), mean±SD	66±9	67±9	66±10	0.441
Male, n (%)	29 (73)	16 (80)	13 (65)	0.288
Persistent AF, n (%)	8 (20)	6 (30)	2 (10)	0.114
Hypertension, n (%)	35 (87)	19 (95)	16 (80)	0.151
Diabetes, n (%)	2 (5)	1 (5)	1 (5)	0.526
CAD, n (%)	8 (20)	5 (25)	3 (15)	0.429
LA (mm), mean±SD	40±5	40±4	40±5	0.951
LVEF (%), mean±SD	62±4	61±5	63±3	0.400
No. of AAD, median	1 (0; 1)	1 (0; 1)	1 (0; 1)	0.204

AAD, antiarrhythmic drugs; AF, atrial fibrillation; CAD, coronary artery disease; CB, cryoballoon ablation; LB, laser balloon ablation; LA, left atrium; LVEF, left ventricular ejection fraction.

patient was excluded from the subsequent analysis.

Post-Ablation Voltage Measurements As a first step, each PV ostium was defined. Considering the multiple angulations of the electroanatomical map, the PV to LA junction (e.g., PV ostium) was defined by points at the maximal inflection between the PV and the LA wall.¹³

The level of ablation scar was quantitatively assessed offline by measuring the LVAs using the NavX™ system. The following parameters were measured with an implemented software tool allowing for exact determination of the map's surface area within an area of manually selected points (**Figure 1**). (1) The left and right isolated antral surface areas (IASA-L and IASA-R; cm²) were defined as the LVAs around the ipsilateral PV ostia. As a sum, the total IASA (IASA-T=IASA-L+IASA-R cm²) was calculated. (2) In order to determine the size of the non-ablated LA posterior wall area (LA PW, cm²) horizontal lines between the most cranial and most caudal points of the LVA around the PV ostia delineated the respective borders of the LA PW. The area between these lines and the posterior border of the LVAs was subsequently assessed. (3) To account for differences in the baseline ASA, the relative size of the LVA (i.e., the isolated surface (ISA) was computed using the following formula: $ISA (\%) = IASA-T / (IASA-T + LA PW) \times 100$. (4) The diameters of the PV ostia were measured (mm) on PV angiography and in standard projections (RAO 30°; LA 40°).

Two independent electrophysiologists blinded to the respective technology used and blinded to each other repeated the measurements twice. Inter- and intra-observer variability was assessed thereafter.

In order to assess a correlation between ISA and clinical outcome, we divided our study population into 2 groups (ISA ≥55%; ISA <55%), based on the results of a recent study that found a better prognosis in patients with a larger ISA (≥55%) after RF PVI ablation.¹³

Post-Procedural Care

After echocardiographic exclusion of pericardial effusion, oral anticoagulation with vitamin K antagonists or a direct anticoagulant was resumed and previously ineffective antiarrhythmic drug therapy was discontinued. For 2 weeks after the ablation, proton pump inhibitor therapy was administered.

Follow-up

All patients were scheduled for outpatient visits including a 72-h Holter ECG at 3, 6 and 12 months. In the case of symptoms suggestive of arrhythmia recurrence, patients were equipped with an external event monitor. An AF recurrence was defined as documented AF episode lasting >30 s.^{1,2}

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 for windows (SPSS Inc., IL, USA). P-values <0.05 were considered statistically significant. Continuous variables are given using mean and standard deviation or median and interquartile range where appropriate. Qualitative variables are shown as frequencies and percentages. Comparisons between groups were performed using t-test (continuous), Chi-square (categorical) and non-parametric rank test (Mann-Whitney U test).

Inter- and intra-observer variability was evaluated using a linear regression model.

To assess if ISA and the clinical success rate were linked, we divided the study population into 2 groups according to ISA size (ISA <55%; ISA ≥55%),¹³ and outcomes in both groups were assessed and compared by means of Chi-square analysis.

Results

Patients' Characteristics

A total of 50 consecutive patients were enrolled in the study. Of them, 10 had to be excluded because LVAs were detected during pre-ablation mapping.

The demographics of the remaining 40 patients are given in **Table 1**. Most were male with a mean age of 66±9 years and in 80% of cases were scheduled for ablation because of drug-refractory PAF. The lowest prevalence of persistent AF was noted in the CB group. Echocardiography revealed normal cardiac dimensions with preserved left ventricular ejection fraction. No significant differences in baseline characteristics were observed between groups.

Mapping Results

The PV sizes were similar in both groups (**Table 2**), except for the RIPV. Of note, 2 patients displayed variant PV anatomy with the presence of a LCPV (n=2 in the LB group).

Table 2. Procedural Data for PV Isolation Using 2 Techniques

	All (n=40)	LB (n=20)	CB (n=20)	P value
Procedural time, min	122±34	141±31	103±24	<0.001
Fluoroscopy time, min	13±4	12±3	14±5	0.148
RSPV size	17±3	17±3	18±3	0.364
RIPV size	17±3	16±3	14±8	0.033
LSPV size	19±3	16±7	14±8	0.055
LIPV size	18±3	18±2	18±3	0.877
LCPV size	27±2	27±2		

LCPV, left common pulmonary vein (PV); LIPV, left inferior PV; LSPV, left superior PV; RIPV, right inferior PV; RSPV, right superior PV. Other abbreviations as in Table 1.

Table 3. Post-Ablation Voltage Measurements of 2 Ablation Techniques

	Remapping data			P value
	All (n=40)	LB (n=20)	CB (n=20)	
IASA-R, cm ²	27±11	22±11	32±9	0.001
IASA-L, cm ²	22±9	19±7	25±10	0.029
IASA-T, cm ²	49±16	42±15	57±14	0.002
PW, cm ²	32±10	34±10	31±10	0.288
ISA, %	60±11	54±10	65±8	0.001

ISA, the isolated surface area; IASA-R, right isolated antral surface area; IASA-L, left isolated antral surface area; IASA-T, total isolated antral surface area; PW, non-ablated LA posterior wall area. Other abbreviations as in Table 1.

After achieving PVI in 100% of cases, a mean of 934 ± 354 mapping points were acquired. IASA-T was significantly larger in the CB compared with the LB group (57 ± 14 vs. 42 ± 15 cm² $P=0.002$; **Table 3, Figures 2B,3**). A significantly wider IASA-R and IASA-L were present in the CB group (IASA-R: 32 ± 9 vs. 22 ± 11 cm² (LB); $P=0.001$; IASA-L: 25 ± 10 vs. 19 ± 7 cm² (LB); $P=0.029$; **Table 3, Figures 2,3**). However, the mean IASA-L was consistently smaller than

the IASA-R in all groups (mean IASA-L 22 ± 9 vs. 27 ± 11 cm²; $P=0.007$). This resulted in statistically significant differences in ISA of $65 \pm 8\%$ and $54 \pm 10\%$ using CB and LB, respectively ($P=0.001$).

Inter-Rater Variability

Linear regression analysis for ISA evaluation demonstrated excellent correlation for inter- and intra-observer variability (inter-observer, LB: $r=0.93$ $P<0.001$; CB: $r=0.88$, $P<0.001$; intra-observer, LB: $r=0.93$, $P<0.001$; CB: $r=0.91$, $P<0.001$; **Figure 4**).

Procedural Data

The mean procedure time, including pre- and post-ablation voltage mapping, was 122 ± 34 min (**Table 2**). It was significantly higher using LB (141 ± 31 min) as compared with CB

(103 ± 24 min; $P<0.001$). Mean remapping time did not differ among the groups (18 ± 3 min). Fluoroscopy time was lower in the LB group compared with CB (12 ± 3 vs. 14 ± 5 min; $P=0.148$, trend).

No periprocedural complications were observed.

Follow-up and Repeat Interventions

During a mean follow-up of 326 ± 142 days, 4 and 5 patients in the CB and LB groups, respectively, experienced an AF/AT recurrence. A total of 3 patients from the LB group, and one from the CB group underwent a repeat ablation

Figure 5. Large and small isolated surface areas (ISAs) in the study population according to ablation technology (**A**) and correlation with clinical success rate (**B**). The majority (95%) of CB patients had a large ISA (>55%). No correlation between large ISA and clinical success rate (AT/AF recurrence after a single PVI procedure) was observed ($P=0.952$). AT/AF, atrial tachyarrhythmia/atrial fibrillation; PVI, pulmonary vein isolation; SR, sinus rhythm.

procedure. PV remapping revealed a LA-to-PV reconnection in 1/12 PVs (8%) in the LB group. All the PVs were chronically isolated in the CB group.

ISA and Clinical Success Rate

Overall, 67% of the patients exhibit a large ISA ($\geq 55\%$; **Figure 5A**) but no differences in clinical outcome were observed between patients with a large ISA ($\geq 55\%$) and patients with a small ISA ($< 55\%$) (**Figure 5B**; $P=0.952$).

Discussion

The goal of the present study was to describe the acute lesion size following balloon-guided PVI using different ablation technologies. For the first time, a prospective comparative analysis was performed using post-ablation electroanatomical voltage mapping. The major findings were: (1) IASA-T was significantly larger after CB-guided PVI compared with LB; (2) this difference resulted from a larger IASA-R around the right PVs; (3) this resulted in an ISA of almost two-thirds of the total antral LA surface area using CB as compared with 54% using LB; and (4) no correlation between ISA and clinical outcome was observed during a 1-year follow-up.

Lesion Location and Differences in IASA

It has been shown in previous studies using RF that the IASA size after circumferential PVI varies substantially and that a large IASA is associated with improved clinical outcome.^{11,13} It is notable that the IASAs found in this study were larger than in previously published studies.^{13,21} This may be the result of different LA sizes and/or differences in the analyses. Kiuchi et al calculated the IASA based on 3D markers arbitrarily taken during the ablation,¹³ but in the present study we used electroanatomical voltage mapping to truly demarcate the acute ablation lesion size. A direct comparison of the absolute numbers should be performed with caution but the present results are intended to provide comparative data on 2 different ablation devices. However, when analyzing the IASA in relation to the LA

map size (e.g., ISA) very similar results were obtained.

Previous observations have shown that balloon-guided PVI creates lesion sets outside the tubular portion of the PV but leaves the antral myocardium rather unaffected, thus being deemed to be truly ostial.¹⁵ This may not apply to the 28-mm 2nd-generation CB, as recently demonstrated by voltage mapping and biomarker release.^{21,22}

According to the present study's results, the 2nd-generation CB enabled more proximal (i.e., antral) ablation lesions involving a large amount of atrial myocardium. These differences might be explained by the exclusive use of the 28-mm CB and the new technical design with a larger zone of cooling. On the other hand, despite the ability to inflate to a maximum of 32 mm the LB created smaller IASAs. It is speculated, that (1) the discrete ablation spots of the diode laser (30° of an arc, width 2 mm; **Figure 2A**) may have provided more discrete lesions and (2) with intent to achieve optimal balloon to tissue contact the operator was biased to choosing a smaller balloon size, resulting in higher conformability (softer balloon).

Unlike in previous studies, the differences in IASA were driven by the larger IASA-R. The anatomical relation of transeptal access to the right PV ostia may explain this. The longitudinal RSPV axis is directed anterior-superior. By pushing the balloon to the RSPV ostium the more proximal CB parts are pushed against the posterior LA wall, creating a broad zone of contact. This is well in line with the results of remapping studies following an index CB-guided PVI, demonstrating that most LA-to-PV reconnections occur at the opposite anterior right PV ostium.²³ In contrast, at the lateral PVs the CB is well aligned with the PV axis.

Clinical Implications

Early studies on the use of the big CB have already indicated the feasibility of antral PVI by reporting the "cross-talk" phenomenon.¹⁷ For the LB a circumferential PVI strategy may be achieved in a subset of lateral but not septal PVs and has been demonstrated to be inferior to a sequential approach.^{24,25} In patients with PAF the durability

of electrical PVI may outweigh the incremental value of more proximal lesions. This explains the remarkable success rates of LB in comparison with CB.²⁶ Moreover, remapping studies after RF-guided procedures report disappointing results, while LB-treated patients display high chronic isolation rates even outperforming the 1st-generation CB.^{14,16,26,27}

In the present analysis, CB-guided ablation gave the largest ISA. However, neither IASA nor ISA was identified as a predictor of clinical success. In this context, it needs to be pointed out that the study was not powered to investigate differences in clinical outcome and that the results may have been confounded by non-homogeneous patient groupings (30% and 10% patients with persistent AF in the LB and CB groups, respectively). Ultimately, only large prospective randomized trials with adequate statistical power will be able to compare clinical outcome between technologies.

In persistent AF a considerable fraction of patients remain free of recurrence after pure PVI (so-called PV responders).^{28,29} In others elimination of extra PV triggers, ganglionated plexi and rotors is desirable. Because many ganglionated plexi and rotors are located in close proximity to the antral PV region large IASAs would be preferable in the treatment of persistent AF. The present data and a recent clinical study suggest the feasibility of using the 28-mm CB even in patients with persistent AF.³⁰ The true value of balloons in this patient population, however, deserves further investigation.

Study Limitations

The sample size of our population was quite small and the study was not powered to investigate differences in clinical outcome.

Finally, the results may have been confounded by the non-homogeneous patient grouping (30% and 10% patients with persistent AF in the LB and CB groups, respectively).

Conclusion

Balloon-guided PVI was associated with antral lesion formation. CB-guided PVI was associated with the largest ISA as compared with LB procedures. ISA size did not correlate with clinical outcome after a single procedure in the present study population.

Funding

The study was supported by a research grant of CardioFocus™.

Conflicts of Interest

L.P. received a grant from the European Heart Rhythm Association. B.S., S.B. and K.R.J.C. have received speakers' honoraria from CardioFocus™; A.F. and K.R.J.C. from Medtronic.

References

- Calkins H, Kuck KH, Cappato R, Brugada J, Camm J, Chen SA, 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. *Europace* 2012; **14**: 528–606.
- Inoue K, Murakawa Y, Nogami A, Shoda M, Naito S, Kumagai K, et al; Japanese Heart Rhythm Society Members. Current status of catheter ablation for atrial fibrillation: Updated summary of the Japanese Catheter Ablation Registry of Atrial Fibrillation (J-CARAF). *Circ J* 2014; **78**: 1112–1120.
- Ouyang F, Antz M, Ernst S, Hachiya H, Mavrikakis H, Deger FT, et al. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: Lessons from double lasso technique. *Circulation* 2005; **111**: 127–135.
- Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J, et al. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation* 2005; **112**: 627–635.
- Cappato R, Negroni S, Pecora D, Bentivegna S, Lupo PP, Carolei A, et al. Prospective assessment of late conduction recurrence across radiofrequency lesions producing electrical disconnection at the pulmonary vein ostium in patients with atrial fibrillation. *Circulation* 2003; **108**: 1599–1604.
- Lee G, Spence S, Teh A, Goldblatt J, Larobina M, Atkinson V, et al. High-density epicardial mapping of the pulmonary vein-left atrial junction in humans: Insights into mechanisms of pulmonary vein arrhythmogenesis. *Heart Rhythm* 2012; **9**: 258–264.
- Pokushalov E, Turov A, Shugayev P, Artyomenko S, Romanov A, Shirokova N. Catheter ablation of left atrial ganglionated plexi for atrial fibrillation. *Asian Cardiovasc Thorac Ann* 2008; **16**: 194–201.
- Po SS, Nakagawa H, Jackman WM. Localization of left atrial ganglionated plexi in patients with atrial fibrillation: Techniques and technology. *J Cardiovasc Electrophysiol* 2009; **20**: 1186–1189.
- Lalani GG, Trikha R, Krummen DE, Narayan SM. Rotors and focal sources for human atrial fibrillation: Mechanistic paradigm with direct clinical relevance. *Circ J* 2014; **78**: 2357–2366.
- Haissaguerre M, Hocini M, Denis A, Shah AJ, Komatsu Y, Yamashita S, et al. Driver domains in persistent atrial fibrillation. *Circulation* 2014; **130**: 530–538.
- Arentz T, Weber R, Bürkle G, Herrera C, Blum T, Stockinger J, et al. Small or large isolation areas around the pulmonary veins for the treatment of atrial fibrillation?: Results from a prospective randomized study. *Circulation* 2007; **115**: 3057–3063.
- Fiala M, Chovančík J, Nevřalová R, Neuwirth R, Jiráský O, Nykl I, et al. Pulmonary vein isolation using segmental versus electroanatomical circumferential ablation for paroxysmal atrial fibrillation: Over 3-year results of a prospective randomized study. *J Interv Card Electrophysiol* 2008; **22**: 13–21.
- Kiuchi K, Kircher S, Watanabe N, Gaspar T, Rolf S, Arya A, et al. Quantitative analysis of isolation area and rhythm outcome in patients with paroxysmal atrial fibrillation after circumferential pulmonary vein antrum isolation using the pace-and-ablate technique. *Circ Arrhythm Electrophysiol* 2012; **5**: 667–675.
- Dukkipati SR, Neuzil P, Kautzner J, Petru J, Wichterle D, Skoda J, et al. The durability of pulmonary vein isolation using the visually guided laser balloon catheter: Multicenter results of pulmonary vein remapping studies. *Heart Rhythm* 2012; **9**: 919–925.
- Reddy VY, Neuzil P, d'Avila A, Laragy M, Malchano ZJ, Kralovec S, et al. Balloon catheter ablation to treat paroxysmal atrial fibrillation: What is the level of pulmonary venous isolation? *Heart Rhythm* 2008; **5**: 353–360.
- Ahmed H, Neuzil P, Skoda J, D'Avila A, Donaldson DM, Laragy MC, et al. The permanency of pulmonary vein isolation using a balloon cryoablation catheter. *J Cardiovasc Electrophysiol* 2010; **21**: 731–737.
- Chun KRJ, Schmidt B, Metzner A, Tilz R, Zerm T, Köster I, 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; **30**: 699–709.
- Fürnkranz A, Bordignon S, Dugo D, Perotta L, Gunawardene M, Schulte-Hahn B, et al. Improved 1-year clinical success rate of pulmonary vein isolation with the second-generation cryoballoon in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2014; **25**: 840–844.
- Schmidt B, Gunawardene M, Urban V, Kulikoglu M, Schulte-Hahn B, Nowak B, et al. Visually guided sequential pulmonary vein isolation: Insights into techniques and predictors of acute success. *J Cardiovasc Electrophysiol* 2012; **23**: 576–582.
- Sanders P, Morton JB, Kistler PM, Spence SJ, Davidson NC, Hussin A, et al. Electrophysiological and electroanatomic characterization of the atria in sinus node disease: Evidence of diffuse atrial remodeling. *Circulation* 2004; **109**: 1514–1522.
- Kenigsberg DN, Martin N, Lim HW, Kowalski M, Ellenbogen K. Quantification of the cryoablation zone demarcated by pre- and postprocedural electroanatomic mapping in atrial fibrillation patients using the 28-mm second-generation cryoballoon.

- Heart Rhythm* 2015; **12**: 283–290.
22. Bordignon S, Fürnkranz A, Dugo D, Perrotta L, Gunawardene M, Bode F, et al. Improved lesion formation using the novel 28 mm cryoballoon in atrial fibrillation ablation: Analysis of biomarker release. *Europace* 2014; **16**: 987–993.
 23. Bordignon S, Fürnkranz A, Perrotta L, Dugo D, Konstantinou A, Nowak B, et al. High rate of durable pulmonary vein isolation after second-generation cryoballoon ablation: Analysis of repeat procedures. *Europace* 2015; **17**: 725–731.
 24. Schmidt B, Metzner A, Chun KRJ, Leftheriotis D, Yoshiga Y, Fuernkranz A, et al. Feasibility of circumferential pulmonary vein isolation using a novel endoscopic ablation system. *Circ Arrhythmia Electrophysiol* 2010; **3**: 481–488.
 25. Wissner E, Metzner A, Reissmann B, Rausch P, Bardyszewski A, Lemes C, et al. Wide circumferential versus individual isolation of pulmonary veins using the endoscopic ablation system. *J Cardiovasc Electrophysiol* 2014; **25**: 253–258.
 26. Bordignon S, Chun KJ, Gunawardene M, Fuernkranz A, Urban V, Schulte-Hahn B, et al. Comparison of balloon catheter ablation technologies for pulmonary vein isolation: The Laser Versus Cryo Study. *J Cardiovasc Electrophysiol* 2013; **24**: 987–994.
 27. Willems S, Steven D, Servatius H, Hoffmann B, Drewitz I, Müllerleile K, et al. Persistence of pulmonary vein isolation after robotic remote-navigated ablation for atrial fibrillation and its relation to clinical outcome. *J Cardiovasc Electrophysiol* 2010; **21**: 1079–1084.
 28. Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the hamburg sequential ablation strategy. *J Am Coll Cardiol* 2012; **60**: 1921–1929.
 29. Tilz RR, Chun KRJ, Schmidt B, Fuernkranz A, Wissner E, Koester I, et al. Catheter ablation of long-standing persistent atrial fibrillation: A lesson from circumferential pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2010; **21**: 1085–1093.
 30. Schmidt M, Dorwarth U, Straube F, Wankerl M, Krieg J, Leber AW, et al. A novel double cryoballoon strategy in persistent atrial fibrillation: A pilot study. *Clin Res Cardiol* 2012; **101**: 777–785.