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CLINICAL RESEARCH
Ablation for Atrial Fibrillation

Image integration increases efficacy of paroxysmal atrial fibrillation catheter ablation: results from the CartoMerge™ Italian Registry

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Aims The aim of this study was to investigate whether circumferential pulmonary vein (PV) isolation guided by image integration improves the procedural and clinical outcomes of atrial fibrillation (AF) ablation in comparison with segmental PV isolation and circumferential PV isolation guided by three-dimensional (3D) electroanatomical mapping alone.

Methods and results Procedural and clinical outcomes of 573 patients who underwent their first catheter ablation for paroxysmal AF between January 2005 and April 2007 were collected from 12 centres. We evaluated three techniques: segmental ostial PV isolation (SOCA group, 240 patients), circumferential PV isolation guided by electroanatomical mapping (CARTO group, 107 patients), and circumferential PV isolation guided by electroanatomical mapping integrated with magnetic resonance/computed tomographic images of the left atrium (MERGE group, 226 patients). Procedure duration proved to be shorter in MERGE group patients than in CARTO group patients ($P < 0.04$), but longer than in SOCA group patients ($P < 0.0001$). During follow-up, atrial tachyarrhythmias relapsed more frequently in SOCA group patients (44.6%) and CARTO group patients (41.7%) than in MERGE group patients (22.6%; $P < 0.0001$).

Conclusion In patients with paroxysmal AF, circumferential PV isolation guided by image integration significantly improves clinical outcome in comparison with both circumferential PV isolation guided by 3D mapping alone and with segmental electrophysiologically guided PV isolation.

Keywords Atrial fibrillation • Catheter ablation • Image integration • Three-dimensional mapping systems

Introduction

Since the discovery of the pivotal role of the pulmonary veins (PVs) in initiating and perpetuating atrial fibrillation (AF), several strategies for performing AF radiofrequency (RF) catheter ablation have been proposed.[1–3] New ablation strategies are mainly based on anatomy and properly require the placement of ablation lesions at well-defined anatomic locations, namely around the veno-atrial junctions.[3–7] However, variations in PV anatomy are common,[8] and a detailed understanding of left atrial anatomy is required in order to maximize the safety and efficacy of the procedure.

Hence, a new technique that enables high-resolution images from magnetic resonance (MR) or computed tomographic (CT) imaging to be integrated into three-dimensional (3D) electroanatomical mapping systems has been introduced into clinical practice.[9–12] To date, the impact of this new technique on the clinical outcome of AF ablation has been demonstrated only in small single-centre series.[13,14]

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The aim of this retrospective, controlled, multicentre study was to investigate whether circumferential PV isolation guided by electroanatomical mapping combined with image integration improves the procedural and clinical outcomes of RF catheter ablation in comparison with segmental PV isolation and with circumferential PV isolation guided by 3D electroanatomical mapping alone in a large cohort of patients suffering from symptomatic drug-refractory paroxysmal AF.

Methods

Patients

The study population consisted of 573 consecutive patients highly symptomatic for documented paroxysmal AF refractory to more than one antiarrhythmic drug who underwent a first catheter ablation from January 2005 to April 2007 in 12 Italian institutions (see Appendix). We considered only paroxysmal AF patients in order to evaluate the efficacy of PV isolation alone.

Three types of catheter ablation technique were included; all aimed to achieve PV isolation documented by the circular mapping catheter: segmental ostial PV isolation (SOCA group, 240 patients); circumferential antral PV isolation guided by 3D electroanatomical mapping (CARTO group, 107 patients); and circumferential antral PV isolation guided by electroanatomical mapping integrated with MR/CT images of the left atrium (LA) (MERGE group, 226 patients).

In order to take in account the experience of each centre, we compare the percentage of ablation performed during the first 14 months of the study period (early phase) and during the last 14 months (late phase) in each group.

This observational study was approved by each institution's review committee, and all patients provided written informed consent to the ablation procedure.

Magnetic resonance/computed tomographic imaging

MERGE group patients underwent Gadolinium-enhanced MR ($n = 45$) or multislice helical CT ($n = 181$) imaging of the LA and PVs in the post-absorptive state within 7 days before RF ablation.

Magnetic resonance studies were performed on a 1.5 T imaging system (ACS Intera™, Philips, Germany; Signa Excite HDx, General Electric Healthcare Technologies, WI, USA). Magnetic resonance angiograms were obtained with a normal-breath fast-field gradient echo imaging sequence in the coronal plane. Acquisition time was ∼40 s. Slices of 1.5 mm thickness were acquired.

Computed tomographic scans were performed with a 16-slice or a 64-slice multidetector—CT (Light Speed Pro, General Electric Healthcare Technologies; Acquilion 64, Toshiba, Tokyo, Japan; Sensation 16, Siemens, Erlangen, Germany) scanner in accordance with the following protocol: a bolus of 130 cc iodate contrast agent was injected intravenously at an infusion rate of 1.2 mL/s. After a 100 s delay, acquisition of the CT data started automatically.

Detector collimation was 8×1.25 mm, and tube voltage was 120 kV at a current of 600 mA during diastole and a reduction of current by 80% for the remaining time of the cardiac cycle in order to reduce the radiation dose by ∼4 mSv. The CT scan was performed by using prospective-gating at the breath-hold in the inspiratory phase in patients in sinus rhythm (75% of the cycle) and without gating in patients in AF.

Electrophysiological study

Prior to the electrophysiological study, transoesophageal echocardiography was performed 24–48 h before ablation in each patient to exclude LA thrombus. Patients were studied in a conscious state; a bolus of pethidine, midazolam, or propofol was administered in the event of intolerable pain during ablation. One quadripolar or decapolar catheter was inserted into the coronary sinus from the femoral, jugular, or antecubital vein. Single or double transseptal puncture was performed, according to the operator's preference, under fluoroscopic guidance. The ablation catheter and decapolar circular mapping catheter (Lasso™, Biosense Webster Inc., Diamond Bar, CA, USA, or Spiral™, St Jude Medical Inc., Minnetonka, MN, USA) were inserted into the LA through one or two long vascular sheaths.

After crossing the atrial septum, an initial intravenous bolus of 100 IU heparin/kg was administered, followed by continuous infusion of 1000 IU/h in order to maintain the activated clotting time between 300 and 400 s.

Integration of magnetic resonance/computed tomographic images into the three-dimensional mapping system

The MR/CT image was imported into a novel version of the electroanatomical mapping system (Carto™ XP, Biosense Webster Inc.) equipped with a custom-designed software (Cartomerge™, Biosense Webster Inc.).

Proprietary software tools on the electroanatomical mapping system allow segmentation of the cardiac image to separate the LA and the PVs from the surrounding cardiac structures. Images of the LA and the PVs were then exported into the real-time mapping system for registration.[11–15]

The CARTO system superimposed the 3D MR/CT LA surface reconstruction onto the real-time LA electroanatomical map by means of two algorithms. The first, called 'landmark registration', approximated the electroanatomical map to the 3D MR/CT surface reconstruction by matching the landmark pairs. The second, called 'surface registration', fitted the 3D MR/CT surface reconstruction to the points on the electroanatomical map by rendering the smaller average distance of the two data sets. Two different registration strategies were adopted, according to the operator's preference.[13,15]

The electroanatomical map was regarded as the gold standard with which the MR/CT accuracy of fit was compared. Closeness of fit was defined in terms of the mean distance between all electroanatomical map points and the 3D MR/CT surface (surface-to-point distance). Individual points with an error >5 mm were deleted.

Catheter ablation

The three catheter ablation strategies were all aimed at obtaining PV isolation documented by the circular mapping catheter. The PV was deemed isolated when PV potentials disappeared or were disconnected (entry block), and when pacing with a stimulus of twice the amplitude of the stimulation threshold and of 2 ms duration from all five bipolar electrodes of the circular mapping catheter enabled local capture without LA capture (exit block).

SOCA group

In SOCA group patients, a decapolar circular mapping catheter and a 3.5 mm cooled-tip ablation catheter (Celsius, Thermocool™, Biosense Webster) or an 8 mm tip ablation catheter (Celsius, Biosense Webster) were inserted simultaneously into the LA. Once the ablation catheter had entered the PV, the circular catheter was positioned as close to the PV ostium as possible. Circular mapping was performed

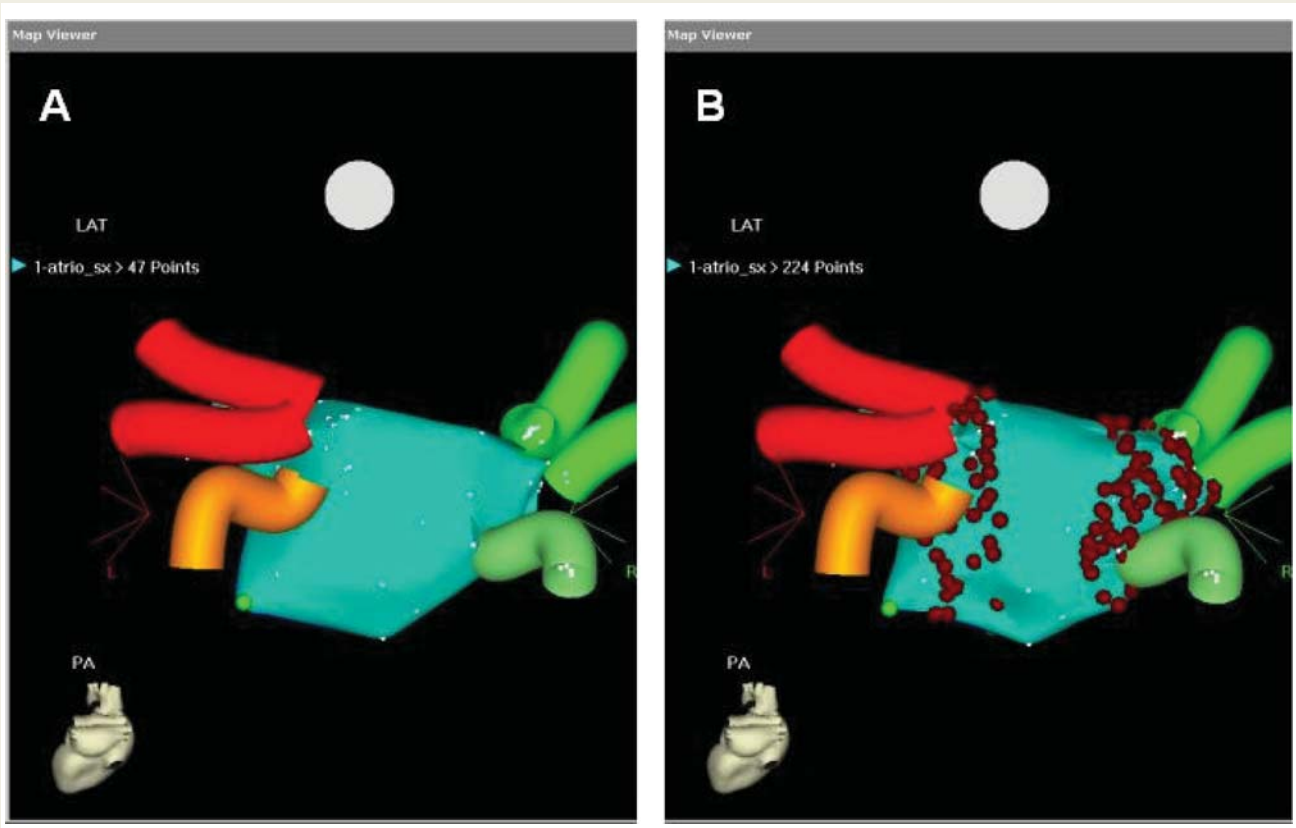

Figure 1 (*A*) Postero-anterior view of the 3D reconstructed electroanatomical map of the LA. Tubes identify PVs. (*B*) The same view after ablation. Red dots identify circumferential lines of ablation around PVs.

by obtaining five bipolar electrograms (1 to 2, 3 to 4, etc. up to 10 for each pair of electrodes) from the circularly arranged electrodes of the mapping catheter. Pulmonary vein isolation was achieved by applying RF at the ostial sites showing electrical breakthroughs.[16] Radiofrequency was applied in a power-controlled mode with a temperature setting up to 45°C, RF energy up to 38 W, and an irrigation rate up to 30 mL/min, while using the 3.5 mm cooled-tip catheter; in the case of the 8 mm tip catheter, the temperature was set up to 55°C and RF energy up to 60 W.

CARTO group

For circumferential PV ablation guided by 3D electroanatomical mapping, once the mapping catheter (Navistar ThermoCool, Biosense Webster Inc.) had been inserted into the LA, mapping of the LA was performed as described previously.[17]

Radiofrequency pulses were delivered by means of a 3.5 mm cooled-tip catheter (Navistar ThermoCool, Biosense Webster Inc.) in a power-controlled mode, as described above. The aim of RF applications was to reduce local bipolar voltage either by 80% or to <0.1 mV at the ablation sites.[3] The ablation strategy consisted of creating contiguous focal lesions at a distance ≥5 mm from the ostia of the PVs, thereby forming a circumferential line of conduction block around each PV or around ipsilateral PVs according to the anatomy (*Figure 1*).[17] On completion of circumferential ablation, a decapolar circular catheter was placed at the PV ostium for PV potential mapping. If PV potentials were still present, segmental ostial ablation targeting the electrical breakthroughs was performed under the guidance of circular mapping, with the aim of PV isolation.

MERGE group

For circumferential PV isolation guided by electroanatomical mapping combined with image integration, image registration was followed by RF pulse delivery by means of a 3.5 mm cooled-tip catheter (Navistar ThermoCool, Biosense Webster Inc.) as described above (*Figure 2*). On completion of circumferential ablation, a circular catheter was placed at the PV ostium to map PV potentials, and segmental ostial ablation targeting the electrical breakthroughs was performed.

Follow-up

After RF ablation, heparin infusion was discontinued until the activated clotting time spontaneously fell to <200 s, in order to withdraw the introducers. Heparin infusion was restarted ~2 h later and continued until the normalized ratio was >2.0. Generally, warfarin was discontinued after 3 months in the absence of atrial tachyarrhythmia recurrences. Cardiac rhythm was continuously monitored during the first 36–48 h. On discharge, transthoracic echocardiography was repeated in order to evaluate the mitral valve and the left ventricular ejection fraction, and to exclude the presence of pericardial effusion.

Follow-up examinations were scheduled at 3, 6, 12, and 18 months. At each follow-up examination, the arrhythmia burden was assessed by 24 h ECG Holter or 7-day ECG recording. To ensure equal follow-up periods, follow-up was censored at 18 months.

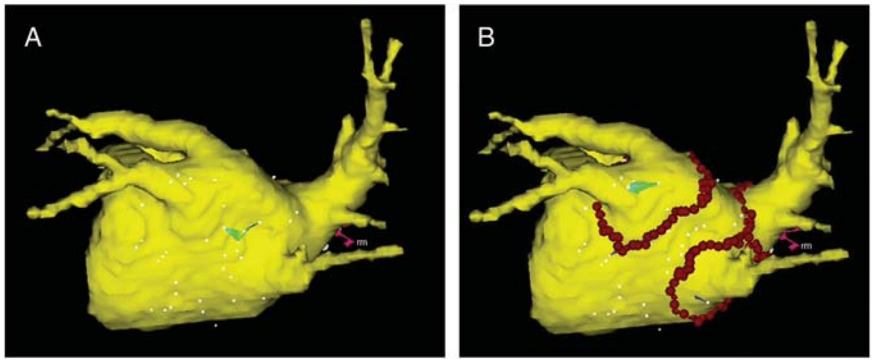

Figure 2 (*A*) Postero-anterior view of the 3D MR LA surface reconstruction. (*B*) The same view after ablation. Red dots identify circumferential lines of ablation around PVs.

Ablation was deemed successful in the absence of symptomatic or asymptomatic atrial tachyarrhythmias >30 s identified on surface ECG, Holter monitoring or 7-day ECG recording, with or without antiarrhythmic drug therapy. As early relapse of atrial tachyarrhythmias within the first 3 months after RF ablation may be a transient phenomenon, this transition period was excluded from the final analysis.[18]

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD (range). Discrete variables are presented as percentages.

Statistical analyses of the variables in the three groups were made by means of Fisher's exact test or χ^2 test for categorical variables, and by means of ANOVA or Kruskal–Wallis test for continuous variables. The normality of distribution of continuous variables was assessed through visual inspection of the histograms. All tests were two-tailed. A *P*-value <0.05 was considered statistically significant.

The actuarial probability of freedom from AF recurrence after ablation was calculated by applying the Kaplan–Meier method separately in the three groups. Differences between the curves were tested for significance by means of the log-rank statistic.

All analyses used the Statistical Package for the Social Sciences (SPSS, version 11.0) (SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics

The clinical characteristics of the 573 study patients are presented in *Table 1*. The three groups did not differ significantly, apart from a lower prevalence of structural heart disease in SOCA group patients.

Procedural outcome

Procedural outcome is presented in *Table 2*. Of note, ablation was performed during the first 14 months of the study more frequently in SOCA group and CARTO group patients than in MERGE group patients ($P < 0.007$), and the use of 3D electroanatomical mapping (both Carto™ System and CartoMerge™ System) facilitated the identification of supernumerary PVs ($P < 0.0001$). Thus, a higher number of PVs were targeted in MERGE group patients than in the other two groups (MERGE 3.92 $\pm$ 0.57 vs. SOCA 3.74 $\pm$ 0.63 vs. CARTO 3.67 $\pm$ 0.97, $P < 0.03$). The total procedural duration was significantly shorter in MERGE group patients than in CARTO group patients (210.3 $\pm$ 63.4 vs. 231.7 $\pm$ 70.7 min, $P < 0.04$), but longer than in SOCA group patients (184.9 $\pm$ 58.4 min, $P < 0.0001$). However, total fluoroscopy time did not differ among the three groups (SOCA 56.5 $\pm$ 22.5 vs. CARTO 55.0 $\pm$ 25.3 vs. MERGE 54.3 $\pm$ 25.5 min, $P = 0.98$).

According to the proprietary software embedded in the CartoMerge™, the mean distance between the points sampled on the electroanatomical map and the closest 3D CT/MR surface ranged from 1.67 to 2.40 mm in MERGE group patients.

Complications

Major complications occurred in 14 patients (2.4%): vascular accidents in 6; PV stenosis >50% in 4, thromboembolic events in 3, and cardiac tamponade in 1. The distribution of major complications was similar in the three groups (SOCA group 2.1%, CARTO group 3.7%, and MERGE group 2.2%, $P = 0.41$).

Clinical outcome

Arrhythmia burden was assessed at each follow-up visit by means of 7-day ECG recording more frequently in SOCA group and MERGE group patients than in CARTO group patients (28.8, 35.4, and 13.1%, respectively, $P < 0.0001$). Follow-up duration was similar in the three study groups: SOCA group 11.2 $\pm$ 5.2 months, CARTO group 12.3 $\pm$ 5.4 months, and MERGE group 11.2 $\pm$ 4.8 months. During follow-up, atrial tachyarrhythmias relapsed in 107/240 (44.6%) SOCA group patients and in 44/107 (41.7%) CARTO group patients, whereas only 51/226 (22.6%) MERGE group patients experienced recurrences ($P < 0.0001$). Moreover, the success rate without antiarrhythmic drugs proved significantly higher in MERGE group patients than in SOCA group and CARTO group patients (43.4, 35.5, and 29.2%, respectively, $P < 0.006$).

Among patients who suffered relapses, the prevalence of atypical atrial flutter/atrial tachycardia was significantly higher in the CARTO group than in the other two groups (6.5% SOCA group patients, 15.9% CARTO group patients, and 3.9% MERGE group patients, $P = 0.09$).

Table 1 Clinical characteristics

	SOCA (*n* = 240)	CARTO (*n* = 107)	MERGE (*n* = 226)	Total
Male (%)	72.3	84.1	77.3	76.7
Age (years)	57.0 ± 10.9	54.5 ± 10.1	57.0 ± 10.9	56.6 ± 10.8
SHD (%)	21.0*,^	28.3	30.8	26.2
Hypertension (%)	29.5	43.4	40.2	36.3
Previous TE (%)	2.1	3.1	5.6	3.2
Left atrial size (mm)	41.9 ± 6.3	42.4 ± 6.3	42.2 ± 6.2	42.1 ± 6.3
LVEF (%)	58.4 ± 7.2	60.1 ± 6.9	58.9 ± 6.3	58.9 ± 6.8
Ablation performed in the early study period (%)	57.9	52.3	43.4§	51.1

LVEF, left ventricular ejection fraction; SHD, structural heart disease; TE, thromboembolic event.
*$P = 0.05$ SOCA group vs. CARTO group.
^$P = 0.05$ SOCA group vs. MERGE group.
§$P < 0.007$ MERGE group vs. SOCA group and MERGE group vs. CARTO group. LVEF, left ventricular ejection fraction; SHD, structural heart disease; TE, thromboembolic event.

Table 2 Procedural characteristics

	SOCA (*n* = 240)	CARTO (*n* = 107)	MERGE (*n* = 226)	Total (*n* = 573)
Irrigated-tip catheter (%)	96.6*	93.3^	100	97.4
Pre-ablation MR (%)	0§	1.9¶	19.5	8.0
Pre-ablation CT (%)	17.5§	53.5!	80.5	48.9
Procedure duration (min)	184.9 ± 58.4§	231.7 ± 70.7!	210.3 ± 63.4#	204.1 ± 65.1
Fluoroscopy duration (min)	56.5 ± 22.5	55.0 ± 25.3	54.3 ± 25.5	55.3 ± 24.4
PV identified (*n*)	3.93 ± 0.37	4.05 ± 0.71	4.06 ± 0.45	4.00 ± 0.48
RF duration (min)	38.8 ± 14.9§	46.7 ± 19.0!	45.7 ± 14.9	43.0 ± 16.0
PV targeted (*n*)	3.74 ± 0.63**	3.67 ± 0.97^^	3.92 ± 0.67	3.80 ± 0.73
PV isolated (*n*)	3.74 ± 0.61§§	3.52 ± 0.98¶¶	3.79 ± 0.75	3.72 ± 0.75

CT, computerized tomography; MR, magnetic resonance; PV, pulmonary vein; RF, radiofrequency.
*$P < 0.001$ SOCA group vs. MERGE group.
^$P < 0.001$ CARTO group vs. MERGE group.
§$P < 0.0001$ SOCA group vs. MERGE group.
¶$P < 0.0001$ CARTO group vs. MERGE group.
!$P < 0.0001$ SOCA group vs. CARTO group.
#$P < 0.04$ CARTO group vs. MERGE group.
**$P < 0.01$ SOCA group vs. MERGE group.
^^$P < 0.03$ CARTO group vs. MERGE group.
§§$P < 0.05$ SOCA group vs. CARTO group.
¶¶$P < 0.007$ CARTO group vs. MERGE group.

The actuarial curves of freedom from atrial tachyarrhythmias, with or without antiarrhythmic drugs, for each group are presented in *Figure 3*. The cumulative probability of atrial tachyarrhythmia recurrence proved significantly lower in MERGE group patients than in SOCA group and CARTO group patients (*Table 3*).

Discussion

Main findings

In patients with paroxysmal AF refractory to antiarrhythmic drugs, circumferential PV isolation guided by image integration significantly improves clinical outcome in comparison with both circumferential PV isolation guided by 3D mapping alone and segmental electrophysiologically guided PV isolation.

The use of 3D mapping increases total procedural time and does not reduce fluoroscopy exposure.

Clinical value of image integration

The first clinical experiences of image integration for AF ablation stemmed from the pioneering studies of Mikaelian *et al.*,[9] who demonstrated that integrating LA electroanatomical maps into 3D CT LA reconstructions was feasible. Later, the integration of electroanatomical maps into CT/MR images of the LA was validated by several studies.[11,12,15]

'Registration', which is the superimposition of the 3D CT/MR LA image on the real-time electroanatomical map, is indicated as the most critical issue in the entire process of image integration. We calculated that after the registration process, the mean distance between the points sampled on the electroanatomical map and the closest 3D CT/MR surface ranged from 1.67 to 2.40 mm. Such errors may be negligible in the clinical outcome of image-guided ablation. Indeed, two previous studies showed that CT image integration improved the clinical outcome of AF catheter ablation in comparison with circumferential PV isolation guided by 3D electroanatomical mapping alone.[13,14]

However, these were both single-centre studies and enrolled a limited number of patients. Thus, the reproducibility of their results remains unproven. Our data, which were obtained from 573 patients enrolled in 12 centres, confirm that circumferential PV isolation guided by image integration is clinically superior both to circumferential PV isolation guided by 3D mapping alone and to segmental electrophysiologically guided PV isolation.

As yet, the clinical advantage of image integration in AF ablation is limited to improving the long-term maintenance of sinus rhythm. Indeed, the rate of major complications proved to be similar; moreover, fluoroscopy time was not significantly reduced, probably owing to the prolonged duration of ablation. Not surprisingly, the use of image integration to guide AF ablation significantly prolonged the procedural time in comparison with simple segmental electrophysiologically guided PV isolation. However, it should be borne in mind that most of the centres involved in our study were using this technique for the first time and that greater experience may lead to a reduction in procedure duration and fluoroscopy time.

Segmental pulmonary vein isolation vs. circumferential pulmonary vein isolation

The question of whether circumferential PV isolation is superior to segmental PV isolation for AF ablation has not yet been answered.[19–21] Circumferential PV ablation, which combines the elimination of PV and ostial triggers with the disruption of ganglionated plexi and rotor modification, should theoretically guarantee the best result.[3] In our study, the clinical efficacy of circumferential PV isolation guided by electroanatomical mapping was comparable to that of segmental electrophysiologically guided PV isolation. This could be explained by the lower number of isolated PVs recorded in CARTO group patients than in SOCA group patients (3.52 ± 0.98 vs. 3.74 ± 0.61, $P < 0.05$). In contrast, circumferential PV isolation guided by image integration improved clinical outcome in comparison with segmental electrophysiologically guided PV isolation. Since the number of isolated PVs obtained at the end of ablation proved to be similar (3.79 ± 0.75 MERGE group vs. 3.74 ± 0.61 SOCA group), the greater efficacy of image integration may be explained by the possibility of delivering RF to the true PV antrum, thanks to the availability of real images of the LA anatomy.

Conclusions

This multicentre trial demonstrated that circumferential PV isolation guided by image integration is superior both to circumferential PV isolation guided by 3D mapping alone and to segmental electrophysiologically guided PV isolation in the treatment of paroxysmal AF, and that this superiority is independent of the operator's skill. True antral ablation, which eliminates PV and ostial triggers, disrupts ganglionated plexi, and modifies rotors, can only be performed if the LA anatomy is clearly visualized.

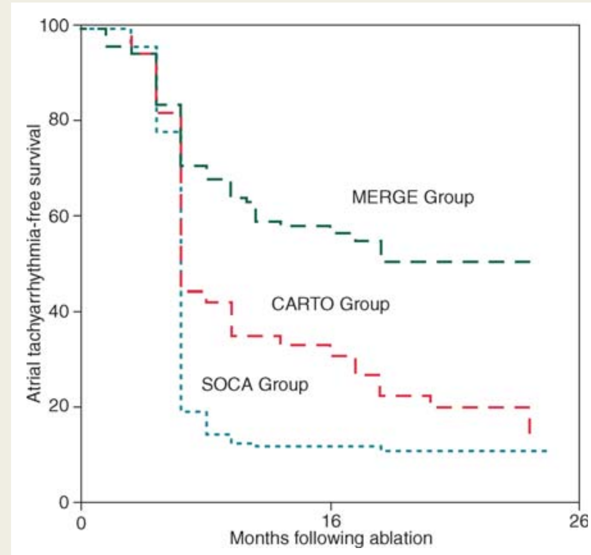

Figure 3 Kaplan–Meier estimation of the time to atrial tachyarrhythmia recurrence after ablation in MERGE group patients (solid line), CARTO group patients (dashed line), and SOCA group patients (dotted line). Log-rank statistic and significance: SOCA vs. CARTO 0.62 ($P = 0.43$); SOCA vs. MERGE 21.45 ($P < 0.00001$); and CARTO vs. MERGE 8.37 ($P < 0.005$).

Table 3 Log-rank statistic and significance of the comparisons among atrial tachyarrhythmia-free survival curves of the three study groups

Group	CARTO	MERGE
MERGE	8.37, $P < 0.005$	
SOCA	0.62, $P = 0.43$	21.45, $P < 0.00001$

Study limitations

The first important limitation is that this was not a randomized study. We cannot, therefore, exclude an enrolment bias, in that the choice of ablation strategy may have been influenced by the patients' clinical characteristics. Indeed, patients who underwent segmental PV isolation displayed lone AF more frequently than those of the other two groups. On the other hand, as segmental PV isolation and circumferential PV isolation guided by 3D mapping alone were more frequently performed during the early phase of the study, a bias related to the different learning curves cannot be excluded.[22] When performing segmental PV isolation and circumferential PV isolation guided by 3D mapping, position of PVs' ostia is unknown, and ablation may be performed within PVs in some patients. However, observational studies like this can provide additional information, since they are fully representative of everyday clinical practice, in which several factors that are underestimated in prospective trials, such as the different experience of the centres involved, may play a role. For this reason, observational studies will be of particular importance in monitoring and guiding the incorporation of this therapeutic procedure into clinical practice.

Asymptomatic AF recurrence could be underestimated during the post-ablation follow-up since the probability of detecting transient asymptomatic arrhythmias increases directly in proportion to the time period monitored, and 7-day ECG recording is more sensitive than 24 h ECG Holter recording.[23] However, in a very recent study, none of the patients with pacemaker documentation of post-ablation AF remained completely asymptomatic during a follow-up period of 1 year.[24] Thus, symptomatic freedom from AF after ablation seems to correlate well with actual freedom from AF after ablation, at least in highly symptomatic patients.

Conflict of interest: E.B. is a consultant of Biosense Webster and Sorin Group. C.T. is a consultant of St Jude and member of the Advisory Board of Biosense Webster. R. De P. is a consultant of Biosense Webster member of the Advisory Board of Biosense Webster. M.G.B. is a consultant of Boston Scientific and St Jude. M.M. is a consultant of St Jude.

Appendix

The following centres and investigators participated in the study (number of patients in brackets): Centro Cardiologico Monzino, Milan: P.D.B., M. Cireddu, G. Fassini, S. Riva, C. Carbucicchio, F. Giraldi, G. Maccabelli, M. Moltrasio, N. Trevisi (116); Istituto Clinico Sant'Ambrogio, Milan: M.M., V. De Sanctis, S. Panigada (90); Azienda Ospedale/Università Santa Maria della Misericordia, Udine: A.P., L. Rebellato (71); Ospedale Civile di Mirano, Venice: E.B., G. Brandolino, F.Z. (59); Ospedale Civile San Camillo-Università Cattolica del Sacro Cuore, Rome: C.T., A. Avella, M. Casella, A.D.R., G. Forleo, F. Laurenzi, A. Pappalardo, G. Pelargonio (46); Università dell'Insubria-Ospedale di Circolo, Varese: R. De P., R. Marazzi, J. Salerno Uriarte (45); Ospedale Santa Maria Nuova, Reggio Emilia: N.B., F. Quartieri (40); Policlinico S. Matteo, Pavia: M.L., C. Belvito, B. Petracci, R. Rodorf, A. Vicentini (30); Ospedale Cisanello, Pisa: M.G.B., G. Arena, R. De Lucia, L. Segreti, E. Soldati, G. Zucchelli (24); Casa di Cura S. Michele, Maddaloni Caserta: G.S., A. De Simone, P. Turco, V. La Rocca, A. Iuliano (23); Ospedale Civile di Conegliano, Treviso: L.C., P. Delise, N. Sitta (22); and Ospedale Civile di Camposampiero, Padua: R.V., M.G. Baccillieri, P. Turrini (7).

Study co-ordinators: E.B., P.D.B., and G.S.

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