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ORIGINAL ARTICLE

Electrographic flow mapping guided catheter ablation offers advantages for patients with persistent atrial fibrillation

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Abstract

Background: Catheter ablation (CA) remains challenging due to suboptimal success rates in persistent atrial fibrillation (AF). Existing mapping technologies cannot reliably distinguish sources in this patient population. Recently, the novel electrographic flow (EGF) mapping system was developed using a modified Horn-Schunk optical flow algorithm to detect and quantify patterns of electrical wavefront propagation in the atria.

Objectives: To test the hypothesis that targeted source ablation based on EGF mapping is superior to empiric AF ablation.

Methods: We included all consecutive patients undergoing EGF guided ablation for persistent AF. All patients underwent pulmonary vein isolation (PVI) and were treated with the same EAM system (CARTO). The outcome of PVI+EGF guided CA was compared with data of PVI-only procedures (PVI-only group) and PVI plus additional empiric adjunctive linear and substrate ablations (PVI+LINES group). 12-months outcome as freedom from AF and atrial tachycardia/flutter (AT/AFL), procedural safety and efficiency characterized by procedure duration, fluoroscopy use, radiofrequency applications and duration, were analyzed. Both intention-to-treat and per protocol analysis were conducted.

Results: A total number of 70 patients (39 in PVI+EGF, 16 in PVI-only and 15 patients in PVI+LINES group) were enrolled. Intention-to-treat analysis showed fewer AF recurrences in PVI+EGF as compared with the PVI-only or PVI+LINES groups at 12 months (25.6% vs. 62.5% vs. 53.3%, $p = .02$). There were no differences in AT/AFL recurrence (17.9% vs. 37.5% vs. 20.0%, $p = .37$). Procedure times were longer in PVI+EGF group ($p < .01$), and there were no differences in fluoroscopy use ($p = .67$).

Conclusion: Our data suggest that patients treated with EGF-guided CA developed fewer AF recurrences. Although the procedure times are longer, it seems to be safe and offers a more targeted, patient-specific ablation strategy beyond PVI than adjunctive empiric lines and substrate ablation in this complex group of patients.

Abbreviations: ACT, activated clotting time; AF, atrial fibrillation; AFL, atrial flutter; AI, artificial intelligence; AT, atrial tachycardia; CA, catheter ablation; CFAE, complex fractionated atrial electrograms; CS, coronary sinus; EAM, electroanatomical mapping; ECG, electrocardiogram; ECV, electrical cardioversion; EGF, electrographic flow mapping; IQR, interquartile range; LA, left atrium; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; PVI, pulmonary vein isolation; RA, right atrium; RF, radiofrequency; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SD, standard deviation; SVC, superior vena cava.

KEYWORDS
catheter ablation, electroanatomic mapping, electrographic flow mapping, persistent atrial fibrillation, pulmonary vein isolation, three-dimensional mapping

1 | INTRODUCTION

Catheter ablation (CA) for pulmonary vein isolation (PVI) has been proven to be the most effective treatment option in symptomatic paroxysmal and persistent atrial fibrillation (AF).[1] However, mid- and long- term success rates of CA for persistent AF remain insufficient.[2] Myriad ablation lesion sets and strategies have been tried in attempts to improve post-ablation outcomes beyond PVI; however, in the absence of a mapping system to identify AF drivers/triggers, these adjunctive ablation strategies such as linear ablation and substrate homogenization have not shown benefit and may instead be pro-arrhythmic as detrimental to overall atrial health. There is growing evidence supporting the presence of self-sustaining extra-pulmonary vein (PV) drivers and/or triggers (AF sources) as explanation for AF initiation and maintenance.[3]

Recently, a novel mapping system—electrographic flow (EGF) mapping was developed using a modified Horn-Schunk optical flow algorithm to detect, integrate over time and quantify patterns of electrical wavefront propagation in the atria. EGF mapping is an innovative method used to approximate cardiac action potential flow through the cardiac chamber that can detect AF sources in patients with persistent AF.

In this study, we aimed to test the hypothesis that source ablation based on EGF mapping is superior to standard three-dimensional electroanatomic mapping (EAM) based PVI-only and/or PVI plus empiric adjunctive linear and substrate ablation strategies in terms of 1-year outcomes of CA for persistent AF. We also assessed procedural times and safety and efficiency.

2 | MATERIAL AND METHODS

2.1 | Primary hypothesis and study design

The local medical ethics committee approved the data collection for this single-center prospective registry (MEC-2019-0023) and concluded that the study did not fall under the Medical Research Involving Human Subjects Act.

Our primary hypothesis was that source ablation based on EGF mapping is superior to PVI-only and PVI plus empiric linear and substrate ablation utilizing a standard three-dimensional EAM system (CARTO, Biosense Webster, Inc., Irvine, CA, USA) in 1-year outcomes of CA for persistent AF. Additionally, we assessed the safety and procedural efficiency of the EGF-guided ablation as compared with standard CA strategies. The primary endpoint of this study was 1-year outcome characterized by AF recurrence during the 12-months follow-up period. The secondary endpoints were atrial tachycardia/atrial flutter (AT/AFL) recurrences, procedure-related major and minor complications, procedure time, radiofrequency applications, ablation time, radiation doses and acute AF termination to sinus rhythm (SR).

This prospective registry included all patients with persistent AF undergoing CA using EGF combined with EAM (PVI+EGF group) between 2018 and 2022. In order to avoid selection bias we included consecutive patients. Primary and secondary endpoint data were compared with data from all consecutive PVI-only procedures using standard EAM (PVI-only group) and PVI plus empiric adjunctive linear and substrate ablations with EAM (PVI+LINES group) performed during the study period treated by the same group of highly experienced electrophysiologists. As inclusion criteria, PVI-only procedures encompass de novo procedures, PVI+LINES and PVI+EGF procedures encompass both de novo and redo procedures.

2.2 | Definitions

PVI was assessed by entrance and/or exit block pacing post-ablation. Acute success of EGF-identified AF source ablation was defined as elimination of the source on post-ablation re-mapping in the same basket position. Total procedure time was defined as the time passed from first puncture until the removal of sheaths. Major complications were defined as any procedure-related adverse events, which were life threatening, required significant surgical intervention, increased hospital admission time or resulted in death. Minor complications were defined as adverse events which resulted in minimal transient impairment of a body function or damage to a body structure, or which did not require any intervention.

Recurrence was defined as AF recorded on a 12-lead electrocardiogram (ECG) or AF lasting > 30 s on a 24-h to 7-day continuous Holter monitoring. AT/AFL recurrence was defined as any AT/AFL documented on 12-lead ECG, or 24-h to 7-day continuous Holter recordings, regardless of its duration.

2.3 | Data collection

Baseline demographic and clinical characteristics from patients were collected from our prospective database using the electronic health records (HiX version 6.2) and analyzed in accordance with the hospital institutional review board policies. Procedural data were derived both from the electronic medical files, as well as from the electronic procedural log files recorded by the Ablamap® system (Ablacon Inc., Wheat Ridge, CO). The following demographic and

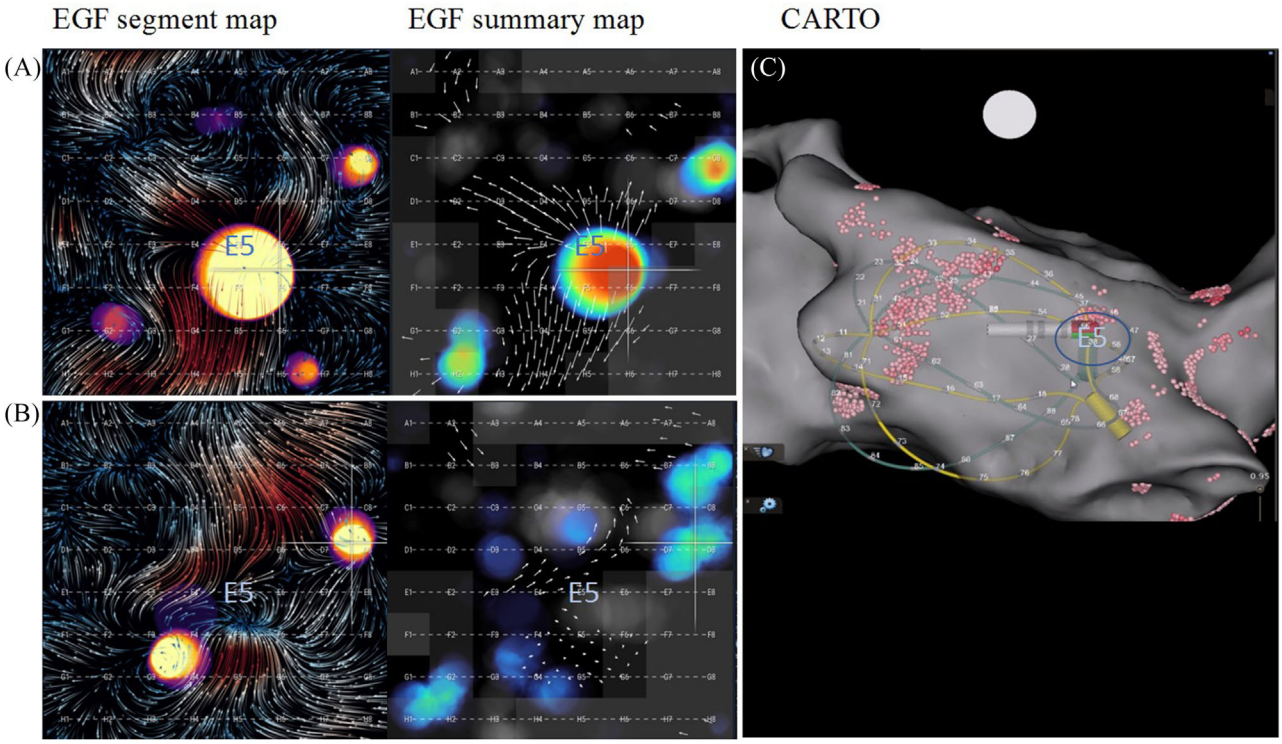

FIGURE 1 Example of de novo AF ablation with EGF mapping. Patient with persistent AF who presented for de novo ablation of AF. After PVI, the patient persisted in AF and thus, EGF mapping was performed. (A) EGF-identified active source was localized to the posterior wall at E5 (red spot). (B) Region around E5 was ablated using a contact force sensing RF ablation catheter and EGF-mapping post-source ablation was performed confirming elimination of the focal source previously detected at E5. Note that after focal source elimination, the pattern of electrographic flow in that region has also changed. (C) Electroanatomic map showing basket catheter position, EGF-identified source location, and ablation application tags including PVI lines. Following the above tailored ablation procedure, the patient remained AF-free at 12-month follow-up. [Color figure can be viewed at wileyonlinelibrary.com]

procedural data were collected from the patients: sex, age, height, weight, BMI, date of procedure, procedure duration time, number of radiofrequency (RF) applications, total RF application duration, radiation dose, AF termination, rhythm at the end of procedure, acute intra-procedural and post-procedural complications. Further, we collected and analyzed clinical data, such as left atrial dimension, left ventricular ejection fraction, comorbidities, and antiarrhythmic medications.

2.4 | EGF and AF mapping

EGF mapping estimates cardiac electrographic "flow" through the atrial myocardium and can detect AF sources in patients with persistent AF.[4] EGF maps are generated from unipolar EGMs recorded from a 64-electrode basket catheter (FIRMap Catheter, Abbott, Menlo Park, CA, USA) over 1 min. The software pre-processes these unipolar EGMs to remove far-field components and normalizes the signals before they undergo flow analysis. The electrical potential profile between the electrode positions at a given point in time is estimated using Green's function assuming micro-electro-neutrality and undisturbed spreading of electrical fields. Using Horn-Schunk flow estimation, these Green's interpolation frames taken every 19 ms are assembled to determine the spatial voltage gradient compared with the temporal voltage gradients derived from each two subsequent frames. The flow vector fields generated by the Horn Schunk algorithm are analyzed to identify singularities where the flow vector angles around a point cover 360 degrees. These singularities are then evaluated for divergence of the flow vector patterns to determine whether the singularity represents an active source (divergent or centrifugal flow vectors) or passive rotational phenomenon (convergent or centripetal flow vectors). Because these origins of EGF often occur repeatedly despite the stochastic variability of the flow fields in AF, this repetitive behavior can be integrated over time and is displayed in the EGF summary map. On EGF summary maps active sources appear redder the higher their rate of detection (or prevalence) and bluer the lower their prevalence. Correspondingly, passive rotational phenomena appear whiter the higher their prevalence and greyer the lower their prevalence (Figures 1 and 2). The percentage of time a source can be detected at its highest intensity in a two second segment is defined as source activity.

2.5 | EGF mapping findings

Patients with EGF-identified stable sources with a source activity above threshold (>26%) were classified as having source-dependent

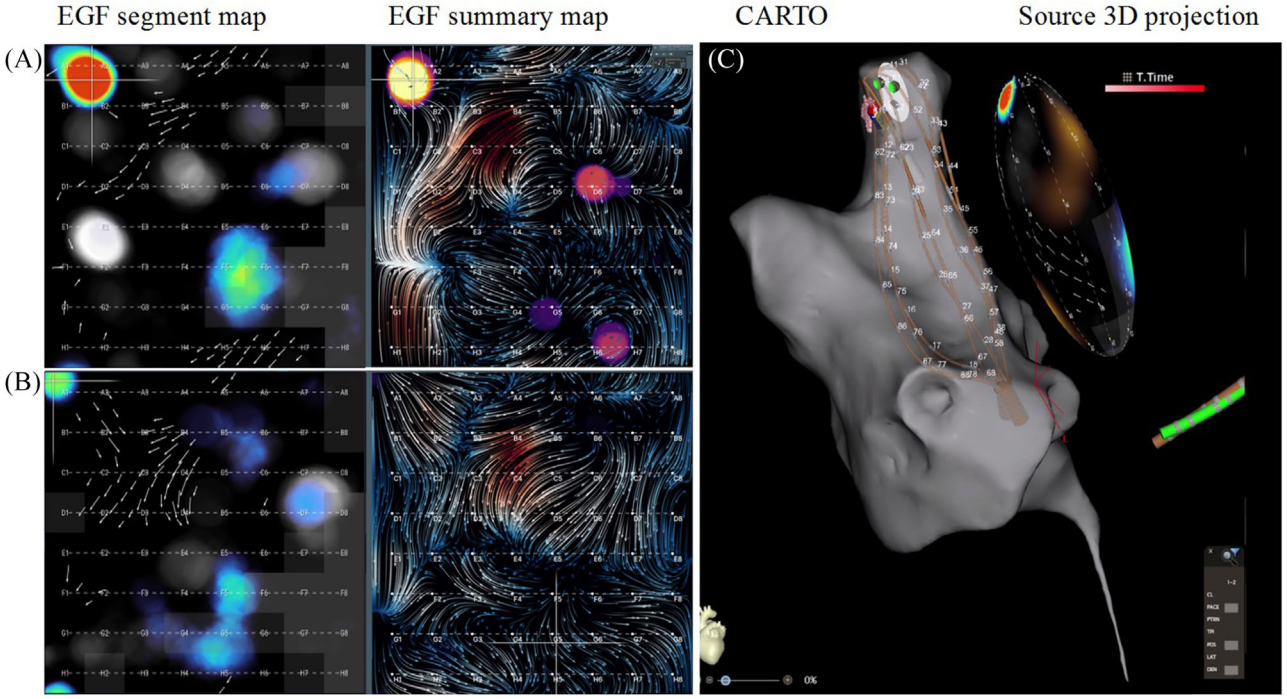

FIGURE 2 Patient with persistent AF who presented for redo ablation for recurrent, symptomatic AF after prior PVI. When pulmonary veins were interrogated, all 4 veins were confirmed to still be isolated from prior PVI. As such, EGF mapping was performed to look for extra-PV sources of AF. (A) An active source was detected in the SVC at AB2 (red spot). (B) Region around AB2 was ablated using a contact force-sensing RF ablation catheter and EGF-mapping post-source ablation was performed confirming elimination of the focal source previously seen at AB2. After focal source elimination, smooth flow is now seen through the region around AB2 that was previously emanating flow. (C) Electroanatomic map showing basket catheter position, EGF-identified source location, and ablation application tags in SVC. To the right of the electroanatomic map is the 3D EGF map showing the relative location of the source within the SVC. [Color figure can be viewed at wileyonlinelibrary.com]

AF (S-Type EGF signature). Patients with no stable active source pattern and no source with activity above threshold were characterized having source-independent AF (C-Type EGF signature). The stratification of patients with S-Type and C-Type EGF signatures has been previously published.[5] Here, we perform a subgroup analysis comparing long-term outcomes data of patients with S-Type EGF signatures versus patients with C-Type EGF signatures.

Based on the above-described classification we conducted an intention-to-treat analysis for the whole patient group ($n = 39$) who underwent EGF mapping and a per-protocol patient analysis ($n = 34$), excluding patients with C-Type EGF signature (no significant sources detected).

We further aimed to illustrate EGF-identified AF sources on a schematic right and left atrial model and draw additional ablation lines performed during empiric ablation (box lesion, wide area circumferential ablation (WACA), roof line, left atrial appendage isolation, anterior line, superior vena cava isolation, and intercaval line) to approximate the percentage of sources covered using empiric/anatomic ablation strategies.

2.6 | CA of persistent AF

Antiarrhythmic drug therapy was not interrupted for patients prior to CA procedures. All CA procedures were performed using the Niobe ES RMN system (Stereotaxis, Inc., St. Louis, MO), under general anesthesia. Vascular access was obtained with femoral venous puncture. A decapolar catheter was advanced into the coronary sinus (CS), and AF was induced with decremental atrial burst pacing in all cases if the patient arrived in the electrophysiology lab in sinus rhythm. To reach activated clotting time (ACT) > 300 sec before the introduction of the basket catheter, intravenous heparin was administered for every patient. Sustained AF of more than 5-minutes duration was recorded using a 64-pole basket catheter (FIRMap™, Abbott, Abbott Park, IL), which was introduced through an 8.5 Fr SL1 sheath in the RA and later into the LA. The basket catheter was introduced into the LA and EGF mapping was performed. Using the EGF mapping software (Ablamap®, Ablacon, Inc., Wheat Ridge, CO), AF sources above threshold were identified and then ablated using a 3.5 mm irrigated-tip catheter (Navistar® RMT ThermoCool®, Biosense Webster). EGF mapping was performed only if all PVs were isolated. In case of re-conducting veins PVI was completed first. Radiofrequency energy was applied with the following power settings: 45–50 W (posterior wall-anterior wall, respectively), temperature limit 43 C, flow rate 17–30 ml/min. Elimination of active sources was confirmed by remapping with Ablamap®. Patients with additional linear ablation underwent stepwise approach: roof line ablation, postero-inferior line ablation, followed by anterior line ablation if no termination or conversion to AT occurred. Electrical cardioversion (ECV) was performed at the end of the procedures when AF persisted after CA.

TABLE 1 Demographic and baseline data.

	All patients ($n = 70$)	PVI+EGF ($n = 39$)	PVI-only ($n = 16$)	PVI+LINES ($n = 15$)	p-value
Age (years)	63.9 ± 7.8	65.0 ± 7.7	60.4 ± 7.6	64.8 ± 6.8	.52
Female (%)	24 (34.3%)	14 (35.9%)	4 (25.0%)	6 (40.0%)	.64
Height (cm)	179.7 ± 9.7	179.6 ± 9.3	183.1 ± 10.4	176.7 ± 8.8	.25
Weight (kg)	91.8 ± 15.6	90.1 ± 13.7	99.6 ± 19.8	87.8 ± 11.8	.24
BMI	28.3 ± 3.8	27.9 ± 3.4	29.4 ± 4.7	28.2 ± 3.7	.39
LA dimension (mm)	46.4 ± 7.0	46.2 ± 7.3	44.9 ± 5.2	46.8 ± 8.1	.79
LA volume (ml)	86.0 ± 17.9	92.9 ± 16.2	74.8 ± 15.8	86.1 ± 19.6	.21
LAVI	42.9 ± 12.4	44.8 ± 14.7	39.5 ± 9.0	43.9 ± 12.2	.54
LVEF (%)	54.0 ± 7.9	53.6 ± 8.2	54.5 ± 7.5	54.6 ± 7.9	.92
TAPSE	20.9 ± 4.4	20.7 ± 4.5	20.9 ± 4.8	21.4 ± 4.2	.91
CHA_2DS_2-VASc score 0 (low risk)	10 (14.3%)	5 (12.8%)	3 (18.8%)	2 (13.3%)	.88
CHA_2DS_2-VASc score 1 (moderate risk)	15 (21.4%)	7 (17.9%)	4 (25.0%)	4 (26.7%)	.88
CHA_2DS_2-VASc score 2 or greater (high risk)	45 (64.3%)	27 (69.3%)	9 (56.2%)	9 (60.0%)	.88
Heart failure	7 (10.0%)	4 (10.3%)	2 (12.5%)	1 (6.7%)	.86
Ischemic heart disease	11 (15.7%)	7 (17.9%)	2 (12.5%)	2 (13.3%)	.84
Hypertension	41 (58.6%)	24 (61.5%)	8 (50.0%)	9 (60.6%)	.72
Cardiomyopathy	2 (2.9%)	2 (5.1%)	1 (6.3%)	0 (0.0%)	.64
Diabetes	11 (15.7%)	8 (20.5%)	3 (18.8%)	0 (0.0%)	.16
Dyslipidemia	3 (4.3%)	2 (5.1%)	0 (0.0%)	1 (6.7%)	.69
CVA or TIA	7 (10.0%)	4 (10.3%)	2 (12.5%)	1 (6.7%)	.86
OSAS	2 (2.9%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	.02
AAD	62 (86.1%)	35 (89.7%)	14 (87.5%)	13 (86.7%)	.93
Previous PVI	22 (31.4%)	16 (41.0%)	0 (0.0%)	6 (40.0%)	<.01

Abbreviations: AAD, antiarrhythmic drug; BMI, body mass index; CVA, cerebral vascular accident; LA, left atrium; LAA, left atrial appendage; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; OSAS, obstructive sleep apnea syndrome; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischemic attack.

2.7 | Follow-up

After each procedure, patients were monitored by 24-h telemetry. Before hospital discharge, regular access site checks, post-procedural echocardiography and ECG recordings were performed to screen for post-procedural complications. Antiarrhythmic medication was unchanged after the procedures, and discontinued after 3 months if no recurrence was documented.

Routine follow-up visits were scheduled in the outpatient clinic of our department for all patients at 3-, 6-, 9-, and 12-months after the procedures. Recordings from 24-h up to 7-days Holter were employed during these visits for documentation of recurrent arrhythmias. For long-term follow-up, patient records were analyzed. We report 6-, 9-, and 12-months follow-up data in this manuscript.

2.8 | Statistical analysis

Data were analyzed using IBM SPSS 25.0 software. Mean and standard deviation (SD) were calculated for normally distributed continuous variables. Median and interquartile range (IQR) were computed for continuous variables with non-normal distribution. Normality was evaluated using the Kolmogorov-Smirnov test. Comparisons between the three study groups were made with one-way ANOVA and Pearson Chi-square test. Descriptive statistics for categorical data were expressed in absolute numbers and percentages. Statistical significance was defined as $p < .05$ (two-tailed). Data showing normal distribution were compared using independent samples t-test, while non-normally distributed variables were analyzed using the Mann-Whitney U-test. The time to recurrence during the follow-up period was tested by the Kaplan-Meier survival curve with log-rank analysis.

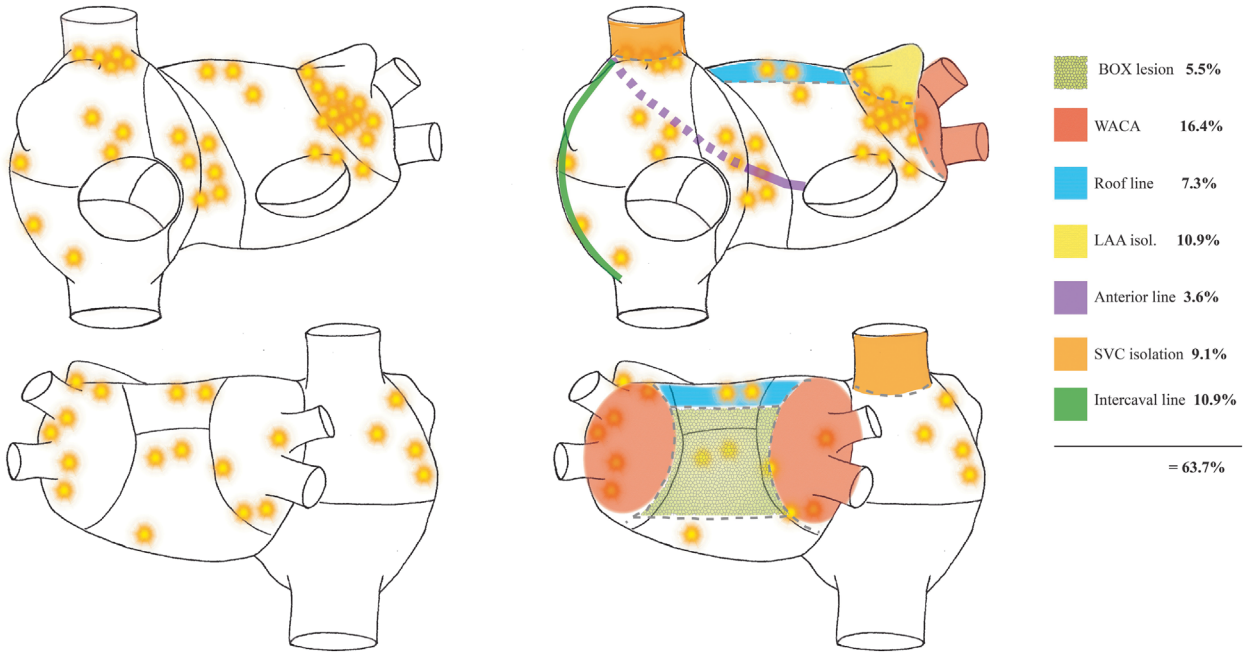

FIGURE 3 EGF source localizations. EGF sources are illustrated on the anterior (upper) and posterior (lower) walls of the right and left atria. For illustrative purposes, the standard locations of empirically performed adjunctive ablation lines, including box lesion, WACA (wide antral circumferential ablation), roof line, left atrial appendage (LAA) ablation, anterior line, superior vena cava (SVC) isolation and intercaval line, are color-coded and superimposed on the biatrial maps of the EGF-identified sources. The percentage of EGF-identified sources that theoretically would be covered by each of these empiric adjunctive lines if every single patient with EGF-identified sources received all of the above empiric adjunctive lesions instead of targeted EGF mapping and ablation are then estimated. [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

3.1 | Demographic and baseline clinical data

A total number of 70 consecutive patients were included in this study (46 male, 34 female). The mean age of the patients was 63.9 ± 7.8 years. Thirty-nine patients were included in the PVI+EGF group; 16 patients in the PVI-only group; and 15 patients in the PVI+LINES group. In the PVI+EGF group, box lesion was performed for 8 (20.0%) patients and PVI or re-isolation/touch-up of the PVs was necessary in 32 patients (82.1%). In the PVI+LINES group, box lesion was performed as empiric ablation for every patient, PVI or re-isolation/touch-up of the PVs was performed in 14 patients (93.3%). Demographic and clinical data are shown in Table 1 and did not demonstrate differences in baseline variables, except the presence of OSAS.

3.2 | EGF mapping data

In the PVI+EGF group, 34 patients had an S-Type EGF signature (87.2%), and 5 patients had a C-Type EGF signature (12.8%). All patients with C-Type EGF signature underwent PV re-isolation, but no further substrate ablation for source-independent AF. Exact AF source localizations identified by EGF mapping are shown in Figure 3. Based on the traditional locations of empiric adjunctive linear ablations that may be performed during an anatomic ablation approach (Figure 4), we found that if all 34 patients in the PVI+EGF group had undergone all of the empiric adjunctive ablation lesion sets shown in the figure, then 63.7% of EGF-identified AF sources could theoretically be eliminated using standard methods.

3.3 | Efficacy of EGF-guided CA: success rates and recurrences

Patients in the PVI+EGF group (*intention-to-treat*) had fewer AF recurrences compared with the PVI-only group and the PVI+LINES group at 6 months (12.8% vs. 50.0% vs. 20.0%, $p = .01$) and at 12 months (25.6% vs. 62.5% vs. 53.3%, $p = .02$). There were no differences in AT/AFL recurrences between the study groups (17.9% vs.37.5% vs. 20.0%, $p = .37$). Comparing data from patients with S-Type EGF signature and C-Type EGF signature in the PVI+EGF group, we found no difference in AF and AT/AFL recurrence (29.4% vs. 0.0%, $p = .30$; 20.5% vs. 0.0%, $p = .56$). Detailed subgroup analysis in shown in Table 2. Detailed follow-up data compared between the PVI+EGF group—*intention to treat*, PVI-only group and PVI+LINES group are shown in Table 3. Detailed follow-up data compared between the PVI+EGF group—*treatment*, PVI-only and PVI+LINES group are shown in Table 4. At the end of the follow-up period 31 patients in the PVI+EGF group (79.5%), 11 patients in the PVI-only group (68.8%), and 12 patients in the PVI-LINES group (80.0%) were under rate-control medication ($p = .66$).

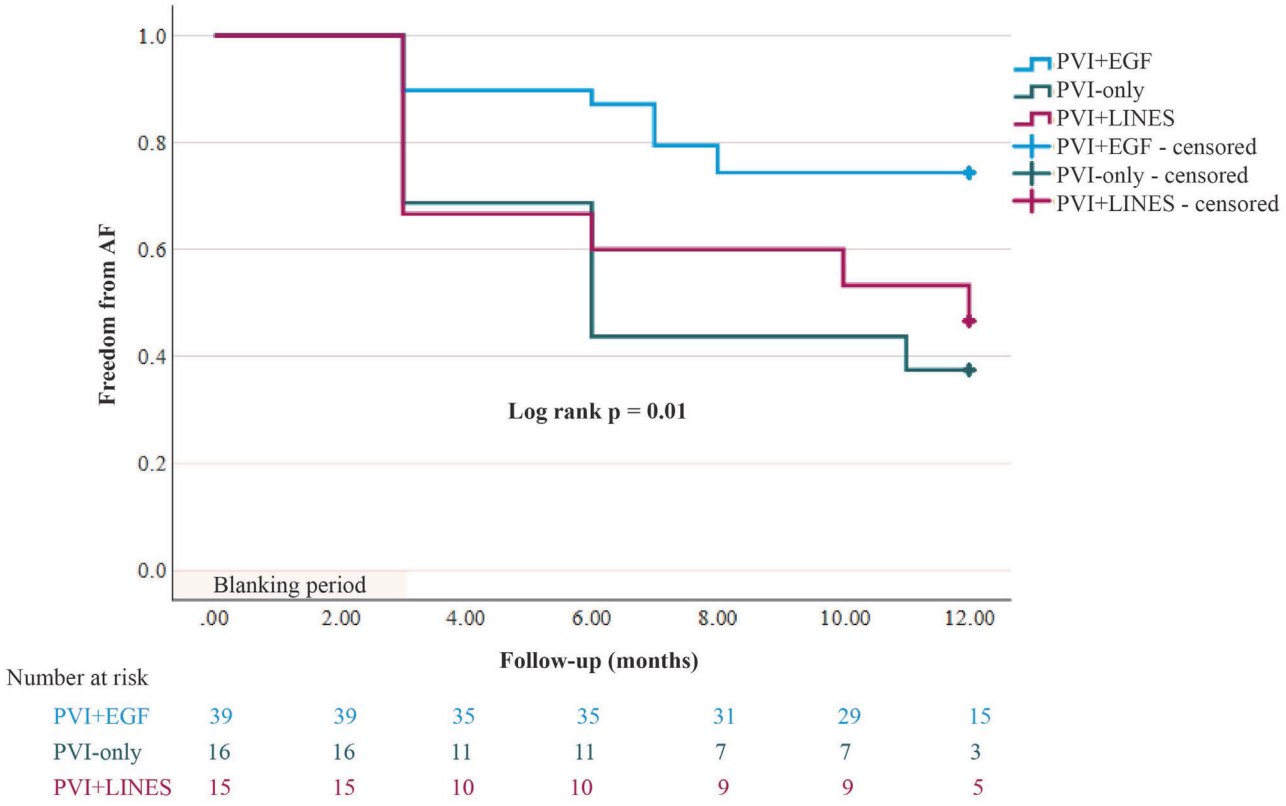

FIGURE 4 Kaplan-Meier survival curve of freedom from AF recurrence in the study groups. PVI+EGF group—patients undergoing PVI plus EGF-guided CA; PVI-only group –; PVI+LINES group—patients undergoing PVI plus empiric adjunctive linear and substrate ablation including a posterior wall box lesion set. PVI plus EGF-guided procedures result in lower AF recurrence rates, compared with PVI-only and PVI plus empiric adjunctive linear and substrate ablation procedures. In this persistent AF patient population, patients undergoing PVI-only procedures showed the highest recurrence rates. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Outcome data S-Type versus C-Type signature.

	S-Type EGF signature ($n = 34$)	C-Type EGF signature ($n = 5$)	*p*-value
Recurrence at 6-months (%)	5 (14.7%)	0 (0.0%)	1.00
Recurrence at 9-months (%)	8 (23.5%)	0 (0.0%)	.56
Recurrence at 12-months (%)	7 (20.5%)	0 (0.0%)	.56
Cumulative recurrence (%)	10 (29.4%)	0 (0.0%)	.30
AT/AFL recurrence (%)	7 (20.5%)	0 (0.0%)	.56

Abbreviation: AT/AFL = atrial tachycardia/flutter.

3.4 | Efficiency of EGF guided versus standard procedures

AF termination during ablation occurred in 1 patient (2.6%) in the PVI+EGF group (*intention to treat*), 1 patient (6.3%) in the PVI-only group and in none of the patients (0%) in the PVI+LINES group ($p = .57$). Comparing AF termination between S-Type EGF signature and C-Type EGF signature patients, we found no difference (0 vs. 1 patient, $p = .12$). Electric cardioversion was performed in 35 patients from the PVI+EGF group, 15 patients from the PVI-only group and 14 patients from the PVI+LINES group ($p = .85$) at the end of the procedure. Procedure times were longer in the PVI+EGF group (189.8 ± 49.7 vs. 130.6 ± 52.5 vs. 146.1 ± 50.9 min, $p < .01$). There were no differences in fluoroscopy use (246.0 vs. 187.5 vs. 202.0 mGy, $p = .67$), RF application number ($p = .07$) and ablation time ($p = .59$) between the three study groups. Procedural data are shown in Table 5.

3.5 | Safety data

We documented hematoma as minor procedure-related complication in one patient in the PVI+EGF group (2.6%). One patient in the PVI-only group (6.3%) on the day of discharge complained about acute pericarditis symptoms without obvious effusion on echocardiography. Anti-inflammatory drugs were administered for this patient (ibuprofen and colchicine), other interventions were not necessary. There were no post-procedural complications in the PVI+LINES group.

TABLE 3 Outcome data intention to treat.

	PVI+EGF ($n = 39$)	PVI-only ($n = 16$)	PVI+LINES ($n = 15$)	p-value
Recurrence at 6-months (%)	5 (12.8%)	8 (50.0%)	3(20.0%)	.01
Recurrence at 9-months (%)	8 (20.5%)	6 (37.5%)	3 (20.0%)	.37
Recurrence at 12-months (%)	7 (17.9%)	5 (31.3%)	7 (46.7%)	.10
Cumulative recurrence (%)	10 (25.6%)	10 (62.5%)	8 (53.3%)	.02
AT/AFL recurrence (%)	7 (17.9%)	6 (37.5%)	3 (20.0%)	.37
Freedom from all arrhythmias	22 (56.4%)	3 (18.8%)	6 (40.0%)	.03
Redo procedure*	1 (2.6%)	6 (37.5%)	5 (33.3%)	<.01
Redo overall	7 (17.9%)	8 (50.0%)	5 (33.3%)	.05

Abbreviation: AT/AFL, atrial tachycardia/flutter.
Redo overall = redo procedure performed during and after the follow-up period.
*Redo procedure during the follow-up period.

TABLE 4 Outcome data treatment.

	PVI+EGF ($n = 34$)	PVI-only ($n = 16$)	PVI+LINES ($n = 15$)	p-value
Recurrence at 6-months (%)	5 (14.7%)	8 (50.0%)	3(20.0%)	.02
Recurrence at 9-months (%)	8 (23.5%)	6 (37.5%)	3 (20.0%)	.47
Recurrence at 12-months (%)	7 (20.5%)	5 (31.3%)	7 (46.7%)	.19
Cumulative recurrence (%)	10 (29.4%)	10 (62.5%)	8 (53.3%)	.05
AT/AFL recurrence (%)	7 (20.5%)	6 (37.5%)	3 (20.0%)	.38
Freedom from all arrhythmias	18 (52.9%)	3 (18.8%)	6 (40.0%)	.07

Abbreviation: AT/AFL, atrial tachycardia/flutter.

4 | DISCUSSION

This is the first human prospective study comparing EGF-guided CA with currently used standard methods. In contrast to the STAR-AF II data that found no reduction in AF recurrence compared with PVI-only when PVI plus adjunctive linear or substrate ablation was performed; our data suggest that PVI plus mapping and ablation of EGF-identified extra-PV AF sources is associated with the lowest recurrence rates in our study groups. Although the implementation of the EGF mapping results in longer procedures, it does not compromise the safety profile of CA procedures and it offers a more targeted, patient-specific ablation strategy that may improve outcomes with respect to freedom from AF at 12-months in an otherwise difficult-to-treat patient population.

4.1 | Ablation of persistent AF

In the current literature, a broad range of success rates is reported after CA for persistent AF.[6,7] Even with the use of modern techniques and technologies, the long-term success rates of PVI-only procedures in patients with persistent AF remains suboptimal and for PVI plus empiric adjunctive ablation such as lines and complex fractionated atrial EGMs, the outcomes are even worse.[8,9] There appears to be a ceiling of efficacy achieved with the PVI-only approach for the treatment of persistent AF. One reason for this may be that patients with persistent AF are more likely to have structural heart disease resulting in more extensive atrial scar and extra-PV triggers. Another reason can be that persistent AF itself causes changes to the atrial myocardial substrate that contributes to recurrent and continuous AF. The optimal ablation strategy might be to detect and eliminate extra-PV sources that initiate AF coupled with an understanding of the individual patient's underlying atrial substrate that maintains AF.

4.2 | Current extra-PV source ablation strategies

The hypothesis that AF may be sustained by localized sources (rotors and focal impulses) was the main topic for many electrophysiology studies and has been widely discussed in the last decade. Early studies suggested that FIRM-guided ablation in addition to standard PVI results in high acute termination rates and high long-term success rates with freedom from AF and AT.[10] Subsequent randomized studies, however, failed to reproduce these early findings.[11] As a standalone procedure, FIRM-guided ablation was insufficient to reduce paroxysmal AF burden.[12]

Complex fractionated atrial electrograms (CFAE) ablation strategy was first described by Nademanee et al. In contrast to circumferential linear ablation, this approach targets CFAE areas in both atria. Initial studies reported high success rates with this strategy, but in later randomized studies CFAE ablation has not been shown to improve ablation outcomes.[13] These studies suggested that ablation of the CFAE alone does not result in organization or termination during ablation.[14] Combining PVI with CFAE ablation initially resulted in possible additional benefits; however, this strategy did not improve persistent AF ablation outcomes.[13,15]

The addition of linear lesions on top of PVI targeting atrial substrate has been investigated since the beginning of CA procedures for AF. Initially, they showed promising improvements in persistent AF ablation outcomes; however, subsequent randomized studies failed to support these initial findings. These studies suggested that the ablation of adjunctive lines is associated with high AT recurrence rates requiring repeat ablation procedures.[16] In addition, in manual CA procedures performing additional lines in the left atrium can be challenging, and it may result in incomplete ablation lines or inability to achieve bidirectional block, further increasing the risk of arrhythmia recurrence. Our findings are consistent with other studies that have shown that performing empiric adjunctive linear ablation does not reduce the recurrence rate significantly compared with PVI-only

TABLE 5 Procedural data.

	PVI+EGF ($n = 39$)	PVI-only ($n = 16$)	PVI+LINES ($n = 15$)	p-value
Procedure time (min)	189.8 ± 49.7	130.6 ± 52.5	146.1 ± 50.9	<.01
Fluoroscopy time (min)	24.0 ± 9.4	21.5 ± 10.2	17.1 ± 9.8	.06
Fluoroscopy dose (mGy)	246.0 (165.0-384.0)	187.5 (96.8 – 400.0)	202.0 (97.0 – 347.0)	.67
Ablation time (min)	29.2 (23.2 - 44.8)	30.3 (18.3 - 41.9)	35.2 (22.6 - 46.1)	.59
Application number	29.9 ± 19.1	19.0 ± 12.1	33.8 ± 22.0	.07
AF termination to SR	1 (2.6%)	1 (6.3%)	0 (0%)	.57
ECV	35 (89.7%)	15 (93.8%)	14 (93.3%)	.85

Abbreviations: AF, atrial fibrillation; ECV, electrical cardioversion; SR, sinus rhythm.

procedures, although these results should be interpreted with caution because of the heterogeneity of the patient population in this study.[9]

4.3 | Identification of AF sources

Significant efforts have been made to define the underlying cellular, molecular and electrophysiological mechanisms that cause the initiation and maintenance of AF. Because AF is a complex arrhythmia that may be the end result of a broad range of pathophysiological processes, identifying AF sources is a great challenge for electrophysiologists. Several approaches have been developed based on phase mapping and activation mapping to tackle this challenge. However, software algorithms based on phase and/or activation mapping suffer significant technical limitations, including poor spatiotemporal resolution, lack of map reproducibility over time, creation of false positives, and the inability to differentiate between active and passive AF sources.[17,18]

Other technologies using global chamber mapping have been introduced, aiming to overcome some of the existing limitations of AF mapping. The Topera mapping system (Abbott/Topera Medical, CA, USA) utilizes the FIRMap catheter to collect electrical activity, and to combine this to an existing geometry created with a 3D mapping system of the atrial chamber. Although the electrical activity can be simultaneously acquired with this system, phase mapping remains limited in terms of the detection of time-dependent relevance and lacks stability over longer recordings or from one recording to the next. A novel dipole charge density based mapping system (AcQMap, Acutus Medical, CA, USA) was developed creating propagation history maps combined with an ultrasound-acquired cardiac chamber anatomy reconstruction. The propagation history maps identify and locate the discrete and coupled mechanisms responsible for the initiation of AF. This mapping technology seems to have promising initial results in the identification of complex AF patterns; however, large multicenter randomized controlled trials are still underway to assess the efficacy of this method.[19] Two prospective, single-arm, international multi-center and nonrandomized clinical studies (UNCOVER-AF, NCT02825992; and RECOVER-AF, NCT03368781) addressed both procedural and long-term outcomes of CA in patients with persistent AF guided by this mapping system.[20]

A novel artificial intelligence (AI) based mapping system (VX1, Volta Medical, Rhode Island, USA) is being developed, aiming to provide real-time analysis of the patient's EGMs to identify dispersed EGMs, and cycle length estimations from EGMs recorded with the mapping and CS catheters. The VX1 software may be used as a support to assist EGM-based CA of AF. An international, multi-center trial (TAILORED-AF, NCT04702451) is being conducted comparing the VX1 software ablation strategy with currently used conventional approaches.

4.4 | EGF mapping in persistent AF

Early studies show that EGF mapping identifies the majority of AF sources detected during the previously described FIRM-guided ablation, but 40% of these sources were actually passive flow phenomena and not active sources of EGF. EGF mapping is the first technology to discriminate active and passive rotational electrical activity during endocardial mapping.[4] As such, this technology may eliminate the unnecessary ablation of passive structures that do not contribute to AF initiation and maintenance and may improve post-ablation outcomes by identifying active AF drivers and/or triggers that may then be targeted for ablation. EGF mapping enables the spatial and temporal reconstruction of electrographic potentials derived from endocardial unipolar EGM data.[21] The inter-procedural reproducibility and spatiotemporal stability of EGF maps and EGF-identified sources suggests that signal acquisition using a basket catheter is sufficient for the localization of AF sources.[22] Its ability to classify AF as being source-dependent (S-type EGF signature) versus source-independent (C-type EGF signature) may be clinically useful for patient stratification and ablation strategy planning.[5] Using this technology, active non-PV drivers and/or triggers of AF can be detected and targeted with ablation to improve long-term outcomes. Our study is the first-in-human prospective study comparing EGF-guided CA with standard PVI-only and PVI plus empiric substrate ablation methods. Our EGF maps showed unexpectedly diverse localization of the detected sources (Figure 3). We cross-matched this with a hypothetical scenario of applying additional ablation lines to our patients and acknowledged that almost 40% of these sources could not have been eliminated by standard ablation lesion sets. Moreover, our results suggest that using EGF mapping might offer advantages and might be beneficial for

patients in terms of long-term outcome and recurrence rates (Figure 4). A randomized controlled clinical trial (FLOW-AF, NCT04473963) conducted at 4 centers has completed enrollment and will evaluate the reliability of EGF mapping to identify AF sources and guide CA in patients with persistent AF.

4.5 | Study limitations

The two main limitations of our study is the low number of included patients and the heterogeneity of the patient groups; however, considering that our study assesses the efficacy of a novel mapping system, which has only been made available in a few medical centers worldwide, the patient population we report on in this paper represents the largest study population using the EGF mapping technology outside of the randomized controlled FLOW-AF clinical trial. This study was not randomized but represents a real-world population of persistent AF patients undergoing CA. Due to the heterogeneous pool of de novo and redo patients our results should be interpreted with caution. Based on this, at this stage we only drew conclusions on recurrence rates in PVI+EGF and PVI+LINES patient groups. Furthermore, the use of a basket catheter can create non-uniform electrode contact with the atrial wall resulting in low intracardiac signal-to-noise ratios that may in some instances affect EGF estimation, particularly in regions where multiple electrodes suffer poor wall contact. In our manuscript we report relatively long procedure times and fluoroscopy duration in the PVI-only group. The reason for this is the following: As an academic center we train several EP fellows every year, PVI only procedures are the first procedures the fellows are allowed to perform more independently, this could result longer procedure- and fluoroscopy times.

5 | CONCLUSION

Our data suggest that persistent AF patients treated with PVI combined with EGF mapping and ablation have less AF recurrences at 1-year. The procedure is safe and may offer a more targeted, patient-specific ablation strategy beyond PVI than adjunctive empiric lines and substrate ablation in this complex group of patients. Clinical utility of this method needs to be further evaluated in a multicenter study with larger patient population.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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