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CLINICAL RESEARCH

Interventional management of recurrent paroxysmal atrial fibrillation despite isolated pulmonary veins: impact of an ablation strategy targeting inducible atrial tachyarrhythmias

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Aims Pulmonary vein isolation (PVI) is an effective treatment option for paroxysmal atrial fibrillation (PAF). Reconnection of pulmonary veins (PVs) is the predominant cause for recurrence of PAF. However, treatment of patients with recurrence of PAF despite isolated PV in the absence of extra-PV foci remains challenging.

Methods and results Of 265 patients undergoing repeat catheter ablation (CA) for recurrence of PAF 21 (8%) patients (14 men, age 58 ± 14 years) showed no reconnection of PV. Therefore, inducibility of sustained atrial arrhythmias was tested. If sustained atrial fibrillation (AF) or sustained atrial tachycardia (AT) was induced, patients underwent CA. During follow-up (FU), Holter- and Tele-electrocardiogram were performed. In 19 (91%) of 21 patients, sustained atrial arrhythmias [16 (84%) AF; 3 (15%) patients AT] were induced. One patient showed PAF. Eighteen patients underwent CA aiming for termination of induced arrhythmia. In 14 (77%) patients, termination into sinus rhythm was achieved. Despite extensive CA, three (16%) patients were externally cardioverted. No periprocedural complications occurred. During 21.2 ± 6.8-month FU, 10 (53%) patients were free of any arrhythmia. Paroxysmal atrial fibrillation recurred in 4 (21%) and AT in 5 (26%) patients. One patient showed persistent AF. Repeat CA was scheduled and successfully performed for these patients.

Conclusion In patients with recurrence of PAF despite isolated PV, termination of induced atrial arrhythmias can be achieved in most patients by defragmentation and AT ablation. Moreover, this ablation strategy results in favourable mid-term outcome results.

Keywords Paroxysmal atrial fibrillation • Pulmonary vein isolation • Ablation • Inducible atrial tachyarrhytmias

Introduction

Focal activity (FA) originating from pulmonary veins (PVs) plays a dominant role in the onset and maintenance of paroxysmal atrial fibrillation (PAF). Therefore, antral pulmonary vein isolation (PVI) has become a curative treatment option for patients suffering from PAF.[1,2] The endpoint of electrical isolation of PV in PAF achieves high acute success rates but long-term results still remain unsatisfying.[3–6] Therefore, reconnection of previously isolated PVs is the presumed cause for recurrence of PAF. Thus, patients with recurrence of PAF after previous successful PVI are usually scheduled for repeat catheter ablation (CA) assuming PV reconnection.[7,8] However, if repeat invasive electrophysiological study (EPS) reveals no reconnection of PV using a circumferential mapping catheter, pharmacological provocation manoeuvre might be performed to reveal dormant PV conduction or extra-pulmonary focus.[9–11] If latter are detectable ablation target and strategy is defined. In case of excluded extra-pulmonary focus or dormant PV reconnection,

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What's new?

- Unique evaluation of particular PAF patients
- Ablation strategies in PAF patients without reconnected PVs
- Distribution of extra-PV AF activity
- Outcome after customized ablation strategy

treatment of these patients can be challenging. Among others, atrial burst stimulation is a frequently used option to provoke arrhythmias in these patients but possibly leads to induction of sustained atrial arrhythmia such as persistent atrial fibrillation (persAF) or atrial tachycardia (AT). Whether induced atrial arrhythmia should be targeted in order to attempt freedom from any atrial arrhythmia remains uncertain in these patients.

Currently, no sufficient data exist on ablation strategies and outcome in patients with recurrence of PAF despite sustained isolation of PVs after previous CA. Thus, the aim of our study was to evaluate the outcome regarding freedom of any atrial arrhythmia after extended mapping and ablation in this cohort targeting induced sustained atrial arrhythmias.

Methods

Study population

From October 2010 until November 2012, 265 patients underwent repeat EP study/CA after previously successful PVI [mean two CA (range one to four)] for documented recurrence of PAF (episode duration <48 h, self-limiting episodes). Antiarrhythmic drug therapy was discontinued at least four half-life prior scheduled repeat CA, and amiodarone was stopped at least 3 months before CA. During CA/EP study in 21 (8%) of these 265 patients, no reconnection of PV was detectable and therefore included in this study. The institutional review committee approved the study and all patients provided written informed consent.

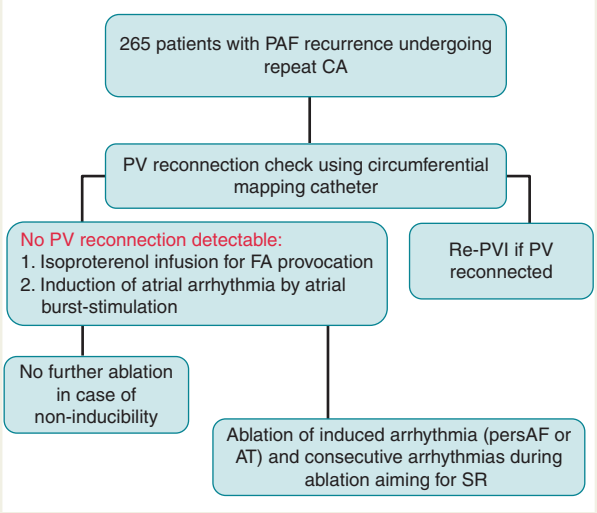

Figure 1 Ablation scheme for patients undergoing repeat CA for recurrence of PAF.

Electrophysiological study and ablation procedure

Prior to the procedure all patients underwent transoesophageal echocardiography to exclude left atrial (LA), in particular, LA appendage thrombi regardless their previous anticoagulant regime. Continuous recording of surface and bipolar endocardial electrograms was performed (Bard Electrophysiology, Lowell, MA, USA). Three catheters were introduced via bilateral femoral vein access: a steerable decapolar catheter (Inquiry, IBI, Irvine Biomedical, Irvine, CA, USA) in coronary sinus (CS) position; for PV mapping a circumferential decapolar diagnostic catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA); and a 3.5 mm irrigated-tip ablation catheter (ThermoCool®, Biosense Webster). Using a single transseptal puncture (TSP) access to LA was achieved and both catheters (Map and Lasso) were placed via the same TSP location. After the TSP and before catheter placement, a first single bolus of 50 IU/kg body weight of unfractionated heparin was administered. Activated clotting time was assessed every 30 min aiming a range of 250–300 s.

The procedure was performed under deep sedation (propofol 1 mg/kg) and supplemental analgesia (sufentanil 0.05 mg) with spontaneous ventilation as previously described.[12] Continuous non-invasive blood pressure and peripheral oxygen saturation measurement was performed for haemodynamic monitoring. In case of significant hypotension, midazolam (0.05 mg/kg) in combination with sufentanil was used. In all patients, a three-dimensional anatomy of the LA (NavX Ensite® Mapping Systems, St Jude Medical, St. Paul, MN, USA) was acquired. After that PVs were checked for possible reconnection (entrance-/exit-block) using a decapolar circumferential mapping catheter and differential pacing manoeuvre to discern far-field signals from actual PV potentials if necessary. After proof of persistent electrical isolated PVs, an infusion of isoproterenol was administered (basal level at 20 μg/min up to 30 μg/min if needed) to reveal extra-PV triggers and provoke FA. In the absence of FA and after attaining baseline heart rate (heart rate before isoproterenol infusion), atrial burst stimulation was performed until the loss of 1:1 capture to induce sustained AF or any other AT. Since, patients suffered from paroxysmal arrhythmias and therefore, documentation potentially revealed AF as well as episodes of an organized arrhythmia, both entities (sustained AF and AT) were targeted when induced.

It should be mentioned that the use of adenosine to reveal possible dormant conduction as a potential predictor of PV-reconnection was omitted since all included patients showed persistent electrical isolation of PVs at the procedure beginning after prior PVI.[13] Furthermore, by the time, the study was conducted no data on routine adenosine application from a larger prospective randomized trial like the ADVICE trial was available to support the use as clinical standard.[14]

If sustained AF (longer than 10 min) or AT was inducible radiofrequency, ablation was performed in the LA, right atrium (RA), and CS using an irrigated ablation catheter (ThermoCool®) with an output up to 30 W (irrigation rate 20–60 mL/min; 0.9% saline infusion using Cool Flow Pump, Biosense Webster) (*Figure 1*). In case of ablation within the CS, a maximum energy amount of 20 W was applied. If sustained AF was induced biatrial mapping and ablation of complex-fractionated atrial electrograms (CFAEs) according to the 'stepwise ablation approach' introduced by Bordeaux group was performed starting in the LA followed by ablation of CFAE in the CS and RA.[15] According to previous studies, CFAEs were defined as areas with low-voltage atrial electrograms between 0.04 and 0.25 mV. The fractionated electrograms preferably were composed of two deflections or more. Also, they showed a perturbation of the baseline with uninterrupted deflection of prolonged activation complexes.[15–21] We defined in case of subsequent ATs after

biatrial defragmentation, or if only macro-re-entrant ATs were inducible mapping and ablation of latter was performed. If necessary, completion of linear lesions, in case of macro-re-entrant aiming for sinus rhythm (SR), was implemented. Possibly created roof and mitral isthmus lines were evaluated by differential pacing manoeuvre.[22–24] Also, a waiting time of at least 15 min was performed after complete line block to reveal early recovery of previously blocked lines. During waiting time repeat atrial burst stimulation with a cycle length (CL) up to 50 ms faster than initial ATCL was performed to test inducibility for similar or further ATs. If induced AF terminated directly into SR during extended ablation, no re-induction was tested, according to the stepwise ablation approach for persistent AF. Termination of sustained AF or AT into SR by ablation was the desired procedural endpoint.

If SR was not achievable after extensive and repeat biatrial defragmentation ablation patients were cardioverted externally to SR using biphasic electro shock with an energy amount up to 200 J. The amount of infused fluids, procedure duration and therefore possible haemodynamic and respiratory impairment were pivotal criteria for stopping procedure before achieving SR.

After a maximum surplus volume balance of 3000 mL saline infusion or no detection of further CFAE signals, as well as a maximum ablation time of 280 min, or observed gradual blood pressure decrease the procedure was stopped and the patient underwent external cardioversion. Patients were discharged off antiarrhythmic drugs (AADs).

Follow-up

All patients were seen every 3–6 months after CA in our outpatient clinic and thereafter every 3 months. Prior to all follow-up (FU) visits, patients received at least two 24-h Holter electrocardiograms (ECGs). Also detailed interrogation for symptoms indicating possible AF or AT recurrence was performed. In case of normal Holter ECG but reported arrhythmia episodes patients received Tele-ECG monitoring to detect short arrhythmia episodes. Oral anticoagulation was continued depending on individual CHA_2DS_2-VASc score and until secure freedom of any atrial arrhythmia was proved. In case of arrhythmia recurrence after a 3-month blanking period, patients were scheduled for a repeat CA.

However, a minimal interval of 3 months was required between the two procedures. Depending on individual symptoms, AAD therapy was restarted until patients underwent repeat procedure.

Statistical analysis

Variables are displayed as mean with standard deviation. Student's *t*-test was used for comparison of patients baseline characteristics. Freedom of any arrhythmia was estimated by the Kaplan–Meier calculation. A *P*-value of <0.05 was considered statistically significant. Analysis was performed using SigmaPlot 12.0 Systat Software, Inc., SigmaPlot for Windows.

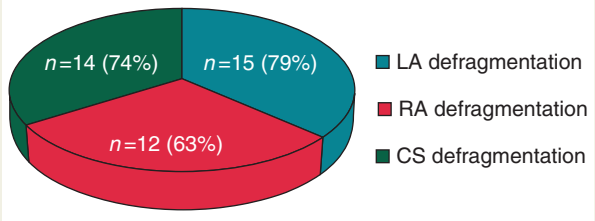

Figure 2 Distribution of defragmentation sites.

Results

Patient characteristics

Patients comprising a total cohort of 265 individuals undergoing repeat CA for recurrence of PAF after initially successful PVI procedures [mean two (range one to four) procedures] were screened. For 21 (8%) patients (14 men; age 58 ± 14 years), no PVI reconnection was detectable. No significant differences regarding baseline characteristics such as sex, age, weight, LA diameter, left ventricular ejection fraction, AF history, or PAF duration were detectable between those patients with reconnection of PV or patients without reconnection of PV despite PAF recurrence. Cardiovascular risk factors or antiarrhythmic drug therapy was comparable in both groups. Antiarrhythmic drugs were suspended at least four half-life prior CA, in case of amiodarone at least 3 months before CA.

Electrophysiological study, ablation, and termination

All patients presented in SR at the beginning of the procedure. After sheaths and catheter placement in 21 (8%) of 265 patients with documented PAF episodes, no reconnection of PVs was detectable using a decapolar circumferential mapping catheter during EP study. After ineffective pharmacological provocation manoeuvres to reveal spontaneously FA in 19 (91%) of these 21 patients sustained atrial arrhythmias were inducible using atrial burst stimulation. Of 19 patients inducible for sustained arrhythmia, 16 (84%) patients showed sustained AF and 3 (16%) sustained left-sided ATs (LA roof dependent). Two patients were only inducible for AF episodes lasting <10 min. The vast majority of patients (84%) was inducible for sustained AF with a familiar distribution pattern of CFAEs (LA roof, septum, left lateral site/mitral isthmus, and LA appendage).

Therefore, these patients underwent biatrial defragmentation ablation (CFAE ablation) in the LA and RA as well as in the CS (*Figure 2*) aiming for termination into SR directly or via prior termination into AT followed by ablation of latter. Overall in 14 (78%) patients, restoration of SR through CA was achieved. In 8 (57%) of 14 patients, a primary termination into SR by CFAE ablation was accomplished. For remaining six (43%) patients, SR was achieved via transient or sustained termination into AT followed by further ablation of these consecutive LA-micro- or macro-re-entries (*Figure 3*).

Despite broad repeat biatrial defragmentation ablation in two (11%) patients inducible for sustained AF, no termination into SR or AT was achieved and therefore both were externally cardioverted into SR after a substantial procedure duration and fluid infusion due to catheter irrigation. All three patients inducible for sustained ATs showed LA roof-dependent flutter and therefore underwent CA aiming for termination into SR by creation of a roofline. Termination of AT into an SR using CA was achieved in all three patients. One patient terminated into perimitral-flutter and one into an LA infero-septal AT during CA for LA roofline block (*Figure 3*). Therefore, CA at the mitral isthmus line as well as ablation at the infero-septal LA was performed to achieve SR. After termination into SR, CA was continued until achievement of a complete block of the roofline and the mitral isthmus line. Afterwards, line block was evaluated by differential pacing manoeuvre. Complete block of the respective lines was achieved in all patients. In the overall

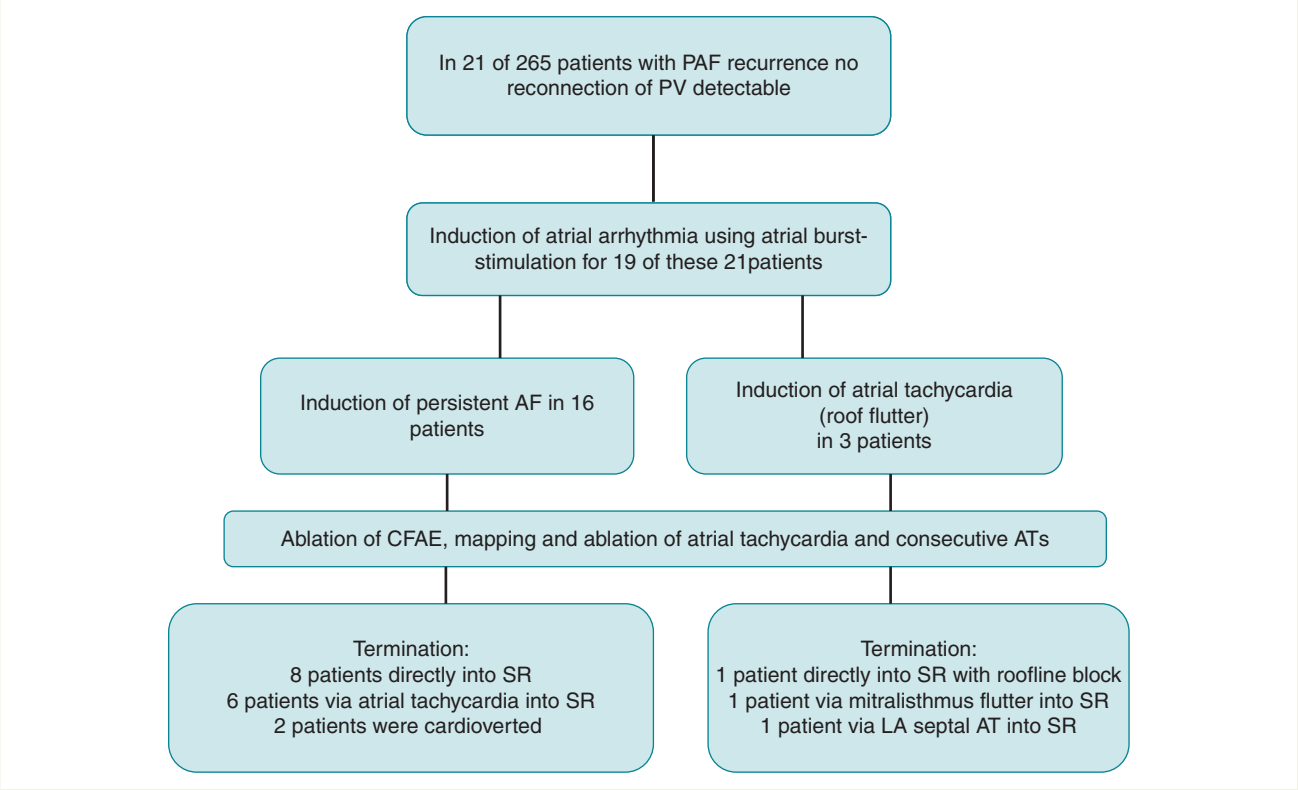

Figure 3 Distribution of inducible arrhythmias and acute ablation outcome.

study population, no major complications such as stroke, atrio-oesophageal fistula, or hemopericardium were observed acutely or during follow-up. The average procedure time was 142.8 ± 64.3 min. The median fluoroscopy time was 31.3 ± 0.7 min with a radiation exposure of 4083.8 ± 5272.2 cGy cm^2.

Follow-up and outcome

The overall FU time was 21.2 ± 6.8 months. Ten (53%) of these 19 patients were free of any AT or AF during FU. All three patients initially inducible for left-sided ATs were free from any further arrhythmia during FU. In four (21%) patients, recurrence of PAF episodes was detectable. Recurrence of AT was observed in five (26%) patients, who initially were inducible for sustained AF and therefore underwent defragmentation ablation. Only one patient showed relapse of persAF. All six patients with recurrence of either AT or persAF were scheduled for repeat CA due to clinical relevant symptom burden and underwent acutely successful repeat ablation.

Discussion

Main findings

In this analysis, we evaluated the effect of an additional CFAE or AT ablation aiming for atrial arrhythmia termination in patients with recurrence of PAF despite persistent isolation of PVs undergoing repeat CA. The presented approach may help to identify a subset of patients with attributing extra-PV factors to the fibrillatory process despite a clinically paroxysmal character of AF. Biatrial defragmentation ablation and CA of potentially consecutive AT, if sustained arrhythmias are inducible, is a therapeutic option in this subset of patients. The overall long-term success rate possibly leads to freedom of any arrhythmia in the majority of these patients.

Complex-fractionated atrial electrogram ablation for paroxysmal atrial fibrillation patients

The benefit of an additional ablation of CFAE beyond only PVI in patients with documented PAF episodes has been discussed controversially.[25–27] In two non-randomized studies, a trend towards a positive benefit for an additional CFAE ablation in both atria was detectable using an automated and therefore more objective CFAE mapping system[28,29] as opposed to an only visual interpretation of CFAE. Earlier studies in animals and human already demonstrated that shortening of the effective refractory period as well as slowing of conduction triggered by AF may beget AF/persAF.[30–33] According to these findings, it has also been shown that ablation of CFAE beyond only PVI in patients with PAF was of substantial benefit.[34,35] Beyond that, Nademanee *et al.*[18,36] were able to achieve good success rates regarding freedom of AF by only targeting CFAE during CA for AF. On the other hand, the most probable trigger for recurrence of PAF is PV reconnection and should be eliminated by PVI only in order to avoid potentially arrhythmogenic extensive biatrial ablation.[1]

However, the summary of all previous results led to assorted recommendations regarding additional CA of CFAE in patients with PAF episodes. More important, it seems that characteristics of the AF population (e.g. LA size, comorbidities, mitral regurgitation, and number of cardioversions) and AF burden (AF duration and AF frequency) are of pivotal significance for an effective ablation strategy and presumably best long-term outcome.[25,26] Therefore, previous data revealed that patients with a higher PAF burden possibly show abnormal atrial substrate changes and therefore may need further CA beyond PVI only.[35,37] Furthermore, AF inducibility after PVI or as performed in this study after proof of persistent PV isolation might help to differentiate patients with PAF in whom further CA ablation/CFAE ablation should be provided.[34,38] In addition, the inducibility of AF using atrial burst stimulation seems to be an adjunct determinant of AF recurrence after successful PVI.[34,39–41] Thus, in this study only patients inducible for AF longer than 10 min or sustained AT received further CA.

Despite this rather aggressive ablation approach, four (21%) patients had further recurrence of PAF episodes. This may be due to the fact that even after repetitive isoproterenol testing some extra-PV foci (EPF) remain unmasked in particular patients comparable with the phenomenon that can be observed in patients with idiopathic ventricular extrasystolia. Therefore, CFAE abolition may be beneficial, not only as areas of slow conduction but also since EPF contributing to spontaneous activity possibly be successfully targeted while mapping and ablating CFAE throughout both atria and the CS.

Distribution of complex-fractionated atrial electrogram and atrial tachycardia mechanisms

If sustained AF (>10 min) was inducible, targeted CFAEs showed a common distribution pattern (LA roof, septum, left lateral site/mitral isthmus, and LA appendage) comparable with the substrate of 'truly' persAF patients as described previously by Nademanee *et al.*[18] and Haissaguerre *et al.*[15] We also assumed that these CFAE regions causing slow conduction and focal (PV like) discharges may arise from these regions and therefore are of importance for AF maintenance.[42] Regarding AT mostly LA roof-dependent flutter was observed as the first inducible AT, this might be explicable since we are in general aiming for a wide antral ablation line around the ipsilateral PVs starting at the LA roof with distinct distance to the PV ostia.

Outcome after complex-fractionated atrial electrogram or atrial tachycardia ablation

As expected the best success rates and long-term results were observed for patients inducible for sustained AT, assuming a more specific target. In 50% of patients inducible for persistent AF, a primary termination into SR was achieved; and for 43%, a termination into AT followed by further ablation into SR was obtained. These high procedural termination rates may be explicable since all included patients presented in SR and only had a history of PAF recurrence and therefore potentially experienced less structural and electrical remodelling than patients solely suffering from persAF.[37,43] However, the inducibility for sustained AF in the study, and therefore performed ablation, might reveal the predisposing substrate ('the second factor') in this cohort to be at the cusp of further electroanatomical changes resulting in solely persAF.[37,44] Therefore, our possibly more aggressive approach appears to be reasonable given the favourable outcome results.

Study limitations

Despite CA some patients still suffered from episodes of PAF revealing the deficiency of an isoproterenol testing or atrial burst stimulation to unmask the responsible EPF for PAF recurrence. Furthermore, not having a comparable group of patients with recurrence of PAF without undergoing this assertive approach may be considered a limitation regarding the spontaneous course and further outcome of these patients compared with our study population. However, all patients in this study were highly symptomatic due to recurrence of PAF episodes despite antiarrhythmic drug treatment and therefore requested further therapy options such as CA. Furthermore, procedure times, fluoroscopy times, and radiation exposure are in accordance with previous studies following the stepwise ablation approach.[15] The use of a semi-automated CFAE detection software may be of substantial value. However, the use of latter was not implemented in our daily routine and ablation procedures following the stepwise ablation approach for persAF.

Conclusion

The recurrence of symptomatic PAF episode in patients not showing reconnection of PVs is rare. However, there is a lack on data how to proceed with this group of patients during repeat ablation. Data of the present study show that, if sustained arrhythmias are inducible in these patients and are targeted for ablation (defragmentation and AT ablation), freedom of any arrhythmia is achievable. Therefore, in the absence of FA biatrial defragmentation ablation and CA for AT can be used as a safe therapeutic alternative, also due to the lack of other options, in patients with recurrence of PAF despite isolated PVIs.

Conflict of interest: none declared.

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