UNIVERSITÉ DE GENÈVE

Archive ouverte UNIGE
https://archive-ouverte.unige.ch

Article scientifique | Article | 2021

Published version | Open Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Significance of post-pacing intervals shorter than tachycardia cycle length for successful catheter ablation of atypical flutter

Dall'Aglio, Pietro Bernardo; Johner, Nicolas; Namdar, Mehdi; Shah, Dipen

How to cite

DALL'AGLIO, Pietro Bernardo et al. Significance of post-pacing intervals shorter than tachycardia cycle length for successful catheter ablation of atypical flutter. In: Europace, 2021, vol. 23, n° 4, p. 624–633. doi: 10.1093/europace/euaa300

This publication URL: https://archive-ouverte.unige.ch/unige:163480
Publication DOI: 10.1093/europace/euaa300

© The author(s). This work is licensed under a Other Open Access license
https://www.unige.ch/biblio/aou/fr/guide/info/references/licences/

ESC European Society of Cardiology
Europace (2021) **23**, 624–633
doi:10.1093/europace/euaa300

Significance of post-pacing intervals shorter than tachycardia cycle length for successful catheter ablation of atypical flutter

Pietro Bernardo Dall'Aglio†, Nicolas Johner, Mehdi Namdar, and Dipen C. Shah*†

Cardiology Division, University Hospital of Geneva, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland

Received 8 September 2020; accepted after revision 8 September 2020; online publish-ahead-of-print 16 November 2020

Aims During entrainment mapping of macro-reentrant tachycardias, the time difference (dPPI) between post-pacing interval (PPI) and tachycardia cycle length (TCL) is thought to be a function of the distance of the pacing site to the re-entry circuit and dPPI < 30 ms is considered within the re-entry circuit. This study assessed the importance of PPI < TCL as a successful target for atypical flutter ablation.

Methods and results A total of 177 ablation procedures were investigated. Surface electrocardiograms (ECGs) were evaluated and combined activation and entrainment mapping were performed to choose ablation sites. Each entrainment sequence immediately preceding static radiofrequency delivery at the same site was analysed. A total of 545 entrainment sequences were analysed. dPPI < 0 ms was observed in 45.3% (247/545) sequences. Ablation resulted in tachycardia termination more often at sites with dPPI < 0 (27.8% vs. 14.5%, $P < 0.001$) and with a progressively increasingly inverse correlation between dPPI duration and ablation success [odds ratio (OR): 0.974; 95% confidence interval (CI) 0.960–0.988; $P < 0.001$]. Tachycardia termination or cycle length prolongation also occurred more often at sites with dPPI < 0 (50.6% vs. 33.2%, $P < 0.001$) and with a similar inverse correlation with dPPI duration (OR: 0.972; 95% CI 0.960–0.984; $P < 0.001$). Twelve-lead synchronous isoelectric intervals were observed in 64.4% (163/253) flutter ECGs and were associated with a dPPI < 0 (75.3% vs. 55.8%, $P < 0.001$).

Conclusion When combined with activation mapping, a negative dPPI is a more effective parameter for identifying a target for successful ablation compared to a dPPI = 0–30 ms. Its occurrence is associated with a critical small narrow slow-conducting isthmus at the target site.

Keywords Atypical flutter • Catheter ablation • Entrainment mapping • Post-pacing interval

Introduction

Despite high-density electroanatomical mapping, radiofrequency ablation (RFA) of atypical flutter (AFL) remains a challenging procedure due to individual variations in the underlying substrate.[1–3] Re-entry circuits result from myocardial diseases, previous surgery or RFA of atrial fibrillation[4–6] and often depend on slow conducting isthmuses.[7]

Entrainment mapping remains a key technique to localize the re-entrant circuit and its different functional segments.[8,9] The difference (dPPI) between the post-pacing interval (PPI) and tachycardia cycle length (TCL) is a function of the distance between pacing site and re-entry circuit.[10,11] Therefore, PPI should be equal to or only slightly longer (<30 ms) than the TCL at sites within the re-entrant circuit. However, the role and significance of negative dPPIs (PPI shorter than TCL) in determining successful target isthmuses for AFL ablation remains unclear.[12]

The objectives of this study were (i) to compare the effectiveness of ablation on entrained sites with dPPI < 0 vs. dPPI = 0–30 ms and (ii)

* Corresponding author. Tel: +41 223727202; fax: +41 223727229. *E-mail address*: dipen.shah@hcuge.ch

† These authors contributed equally to the study.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2020. For permissions, please email: journals.permissions@oup.com.

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022

What's new?

- The addition of entrainment mapping to electroanatomical mapping of atypical flutter leads to a high degree of ablation success.
- Occurrence of a post-pacing interval shorter than tachycardia cycle length (TCL) is a frequent finding and the result of slow conducting properties of the flutter isthmus.
- Sites presenting a post-pacing interval shorter than TCL represent a more effective target for radiofrequency ablation than PPIs of 0–30 ms longer than the TCL.

to compare clinical and procedural characteristics of patients exhibiting entrained sites with dPPI < 0 vs. patients with dPPI = 0–30 ms.

Methods

Patients undergoing catheter ablation of a re-entrant atrial tachyarrhythmia at the Geneva University Hospitals from January 2008 to March 2018 were screened for eligibility. All procedures in which a non-cavotricuspid isthmus (CTI)-dependent atrial macro-reentry was mapped by entrainment and targeted for ablation were included in the study.

Consent

The study complies with the Declaration of Helsinki. Written informed consent was obtained and the study was approved by the institutional review board.

Procedure protocol

Patients underwent routine transthoracic and transoesophageal echocardiography. Femoral venous access was obtained under local or general anaesthesia. Left atrial access was obtained by trans-septal puncture or via a patent foramen ovale. Two decapolar catheters (one steerable with 10–2–10 mm electrode spacing and the other, a fixed curve with 10–5–10 mm electrode spacing, Abbott, Lake Bluff, IL, USA) were advanced respectively in the coronary sinus (up to the great cardiac vein) and in the right atrium (with the tip positioned at the antero-lateral margin of the CTI and the proximal electrode at the superior vena cava-right atrial appendage junction). An open-irrigated tip catheter (Thermocool or Thermocool Navistar or Thermocool SmartTouch, Biosense Webster, Diamond Bar, CA, USA or Tacticath, Abbott, Lake Bluff, IL, USA) was used for mapping and ablation (*Figure 1*). Tachycardia mapping was assisted by electroanatomic mapping (Carto 3, Biosense Webster or Rhythmia mapping system, Boston Scientific, Marlborough, MA, USA) at operator's discretion.

Pacing for entrainment was performed at a cycle length 20 ms below TCL, with bipolar stimulation at 25 mA with 2 ms impulse duration. After confirming entrainment and stable stimulus-to-electrogram intervals, pacing was stopped and PPI measured from the last pacing stimulus to the first deflection of the return electrogram (EGM) on the same bipole (*Figure 2*). Entrainment was first performed from the right atrium decapolar catheter's distal bipole in order to exclude CTI participation in the re-entrant circuit. Additional entrainment was performed as needed from other bipoles of the right atrium and coronary sinus decapolar catheters to derive chamber localization of the re-entrant circuit. Activation rove mapping was performed in the chamber of interest and adjacent areas (e.g. the coronary sinus) to evaluate coverage of the TCL, to localize fractionated EGMs and determine their relationship to the surface electrocardiogram (ECG) isoelectric interval, and to deduce the macro-reentrant circuit as described previously.[13] Three-dimensional activation

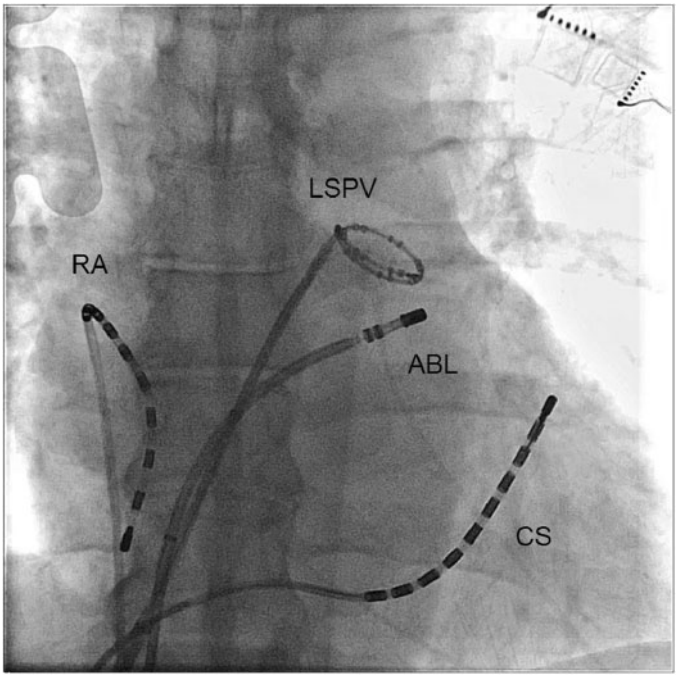

Figure 1 Catheter positions. ABL, ablation catheter; CS, decapolar catheter in the coronary sinus; LSPV, left superior pulmonary vein; RA, decapolar catheter in right atrium.

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022

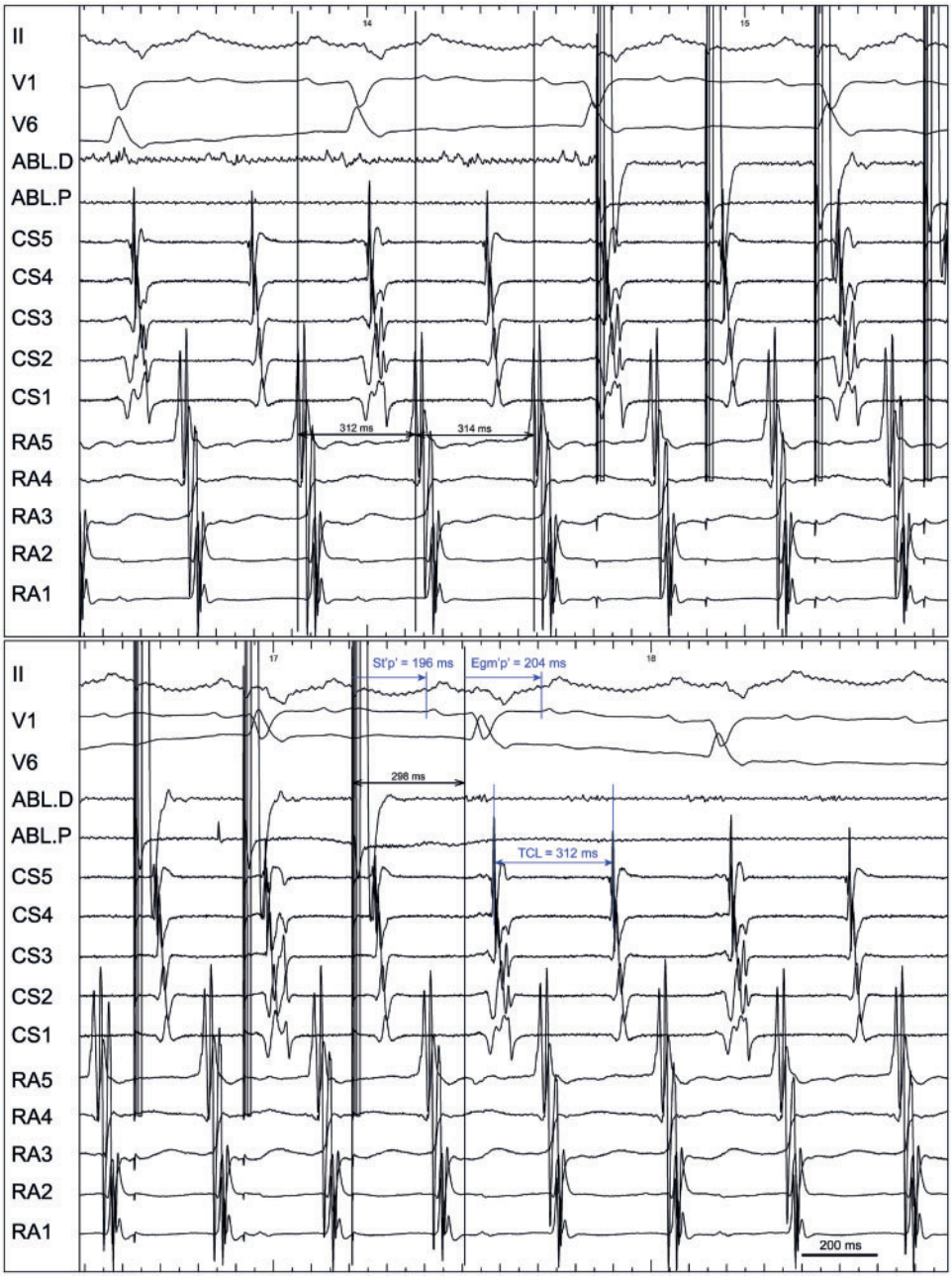

Figure 2 (*Upper panel*) Tachycardia cycle length (TCL) is measured before entrainment (312–314 ms). (*Lower panel*) A short post-pacing interval (PPI = 298 ms), stimulus-to-'p' wave (St-'p' = 196 ms), and electrogram-to-'p' wave (Egm-'p' = 204 ms) intervals are measured at a site of diastolic long duration fractionated potentials over posterior left atrium where flutter was successfully terminated by ablation. Note unchanged electrogram and flutter 'p' wave morphology during pacing indicative of concealed entrainment.

maps were obtained either with the distal bipole of the ablation catheter or with a multipolar catheter (Lasso/Pentaray, Biosense Webster; Orion, Boston Scientific) or both to cover the anatomic entirety of the chamber and >90% of the TCL. Entrainment mapping was performed at putative isthmus sites based upon preliminary entrainment, activation mapping, and EGM fractionation with the aim of choosing the best ablation target. Subsequently, ablation without catheter dragging was performed targeting the narrowest accessible isthmus confirmed by concealed entrainment and dPPI < 30 ms. Radiofrequency power was set at 30–35 W with irrigation at 17–30 mL/min and a temperature limit of 48°C. After achieving tachycardia termination, additional adjacent ablations were delivered to consolidate the lesion and non-inducibility was verified by burst atrial pacing decremented to cycle lengths of up to 200 ms. In case of an anatomically defined isthmus e.g. the left atrium roof or the mitral

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022

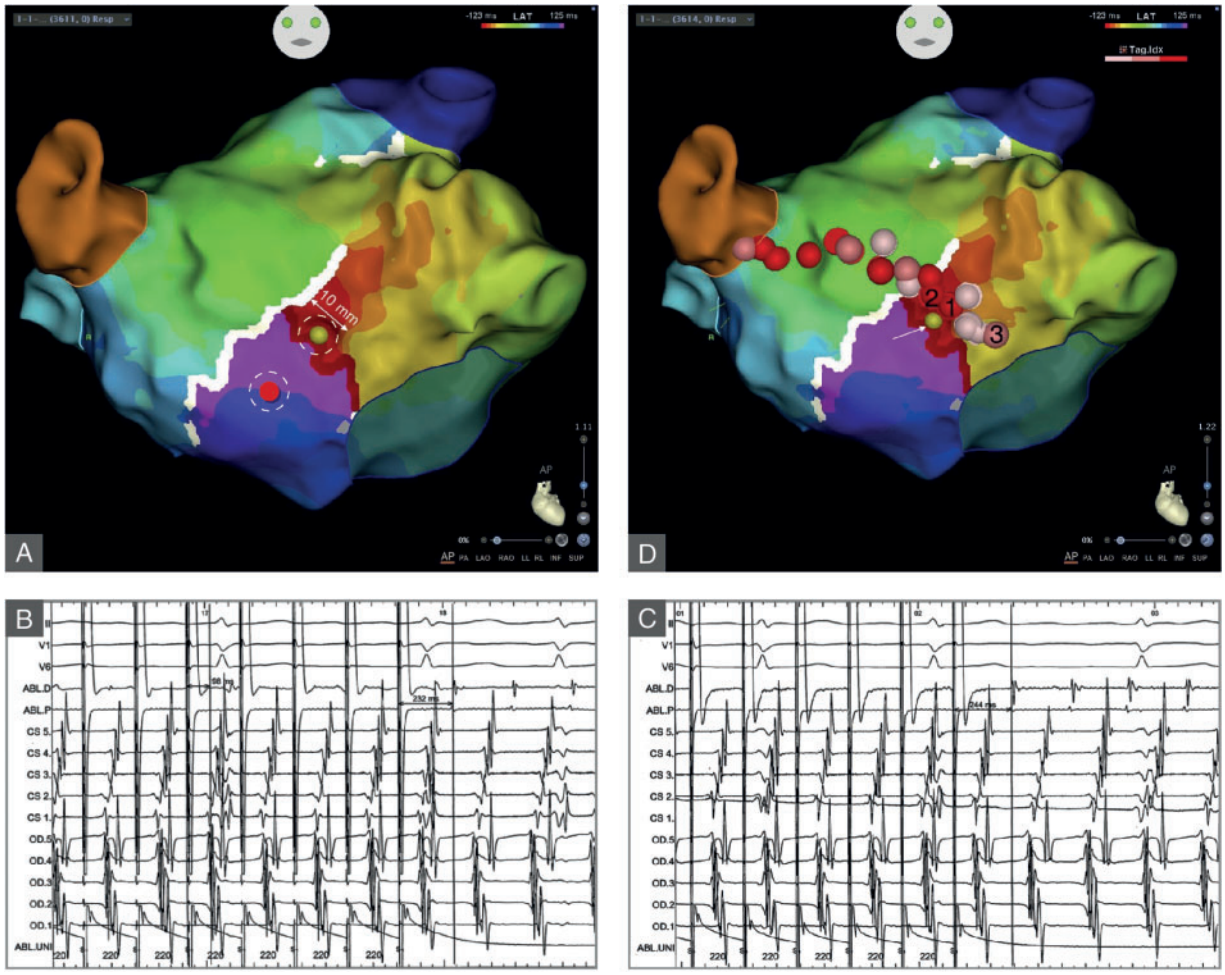

Figure 3 Left atrial activation map colour coded in 15 ms isochronal steps depicting a dominant perimitral flutter with secondary loops (TCL = 252 ms). (*A*) A narrow flutter isthmus (10 mm width) is depicted between two lines of block (the horizontal white line: isthmus superior border; and the segment of the orthogonal red line extending from the yellow isochrone towards the mitral annulus—which represents colliding wave fronts with disparate timing). Entrainment from a narrow isthmus was performed from the yellow dot site. A site at a wider circuit segment and with wide separation of isochrones, where a dPPI 0–30 ms could be recorded is depicted by the red dot. An illustrative approximation of the virtual electrode size, not based on data, is represented by the white dotted lines. (*B* and *C*) Entrainment mapping was performed with different stimulus amplitudes, both resulting in a negative dPPI (*B*: amplitude = 25 mA, PPI = 232 ms, PPI-TCL = −20 ms; *C*: amplitude = 10 mA; PPI = 244 ms; PPI-TCL = −8 ms). (*D*) Ablation lesions superimposed on the previous map (1, 2, and 3: 1st, 2nd, and 3rd ablation targets). The first ablation resulted in cycle length prolongation to 310 ms, the third ablation terminated the flutter after 7.8 s. Ablation line was further prolonged to the right superior pulmonary vein to eliminate a potential second flutter loop.

isthmus, complete conduction block in sinus rhythm was the preferred endpoint (*Figure 3*). Mapping and ablation of other induced AFLs or organized tachycardias was performed at operator's discretion.

Entrainment analysis

All recordings were reviewed offline at a 100 or 200 mm/s sweep speed and measurements performed with an electronic caliper and reviewed by an experienced electrophysiologist. Only entrainment manoeuvres immediately followed by radiofrequency delivery (RFD) at this site were evaluated. Sequences with the following characteristics were included for analysis:

- consistent 1:1 pacing capture and tachycardia acceleration to the pacing rate for the last three pacing stimuli and
- the TCL and activation sequence remained unchanged (<5 ms change) after cessation of pacing.

These sequences were analysed for the following features:

(1) Presence of concealed entrainment based on unchanged surface ECG, intracardiac EGM morphology and activation sequences.
(2) Stimulus to flutter 'p' wave (StP) and electrogram to flutter 'p' wave (EgmP) intervals. Measurements were made from stimulus artefact and from the first deflection of the electrogram to clearly discernible flutter 'p' waves unobscured by QRS complexes or T waves.
(3) dPPI measured from the last pacing stimulus to the first deflection of the return electrogram on the same bipole.
(4) Timing of target electrograms with respect to a 12-lead synchronous surface ECG isoelectric interval during ongoing flutter.

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022

Table 1 Baseline characteristics

Demographics		153 patients
Male gender, *N* (%)		110 (71.9%)
Age (years)		61 (±12)
Hypertension, *N* (%)		72 (47.1%)
Diabetes, *N* (%)		18 (11.8%)
Hypercholesterolaemia, *N* (%)		57 (37.3%)
BMI (kg/m^2)		27.90 (±5.27)
Previous TIA/stroke, *N* (%)		11 (7.2%)
CHA_2DS_2-VASC score, *N* (%)	0–1	66 (43.2%)
	≥2	87 (56.8%)
Structural heart diseases, *N* (%)	58 (37.9%)	
	Myocardial infarction	31 (20.3%)
	Cardiac surgery	32 (20.9%)
	Surgical ablation	10 (6.5%)
Medical history		
Previous ablations, *N* (%)	None	22 (14.4%)
	Atrial fibrillation	97 (63.6%)
	Typical flutter	15 (9.8%)
	Atypical flutter	19 (12.4%)
Antiarrhythmic drug, *N* (%)	Amiodarone	37 (24.2%)
	Sotalol	7 (4.6%)
	B-Blockers	92 (60.1%)
	Flecainide	11 (7.2%)
	Dronedarone	2 (1.3%)
	Propafenone	2 (1.3%)
	Digoxin	17 (11.1%)
	Calcium blockers	14 (14.2%)
Echocardiography findings		
LA diameter (cm)		4.21 (±0.74)
LA surface (cm^2)		25.16 (±6.86)
LA volume (mL)		94.71 (±39.95)
LV ejection fraction (%)		53.38 (±10.32)

BMI, body mass index; LA, left atrium; LV, left ventricle; RA, right atrium; TIA, transient ischaemic attack.

Patients were divided into two groups depending on whether at least one site with a dPPI < 0 was observed during the procedure or not. Each targeted re-entrant tachycardia and entrainment manoeuvre was similarly classified on the basis of the observation of a dPPI < 0.

Surface ECG was evaluated for indications of a narrow slow-conducting isthmus. ECG sequences presenting at least two consecutive flutter 'p' waves unobscured by overlying QRST segments were analysed. Isoelectric intervals were defined as the absence of surface ECG activity for ≥80 ms simultaneously on all 12 leads between two consecutive flutter 'p' waves.[7]

Outcome definitions

Tachycardia termination during RFD at a critical flutter isthmus was considered full ablation success. A sustained increase in TCL (>20 ms) was considered partial success. Procedural success was defined as absence of any sustained flutter induction.

Statistical analysis

Categorical variables are reported as absolute values and percentages. Continuous variables are reported as mean ± standard deviation. Association between categorical variables was assessed with Pearson's χ^2 test or Fisher's exact test. Correlation between continuous variables was tested with Pearson correlation coefficient. Association between normally distributed continuous variables was tested with Student's *t* test. Logistic regression was used to assess the association of a continuous variable with categorical outcome. Mixed effect logistic regression was used to test for independent association in a multivariate model clustering by patient and by flutter. Analyses were performed with SPSS (IBM SPSS 22.0 version statistical software, Armonk, NY, USA) and STATA 15 (StataCorp, College Station, TX, USA).

Results

Overall, 153 patients who underwent 177 procedures were included in this study. Among these patients, 26 had undergone surgery for valvular replacement or repair (17%, followed in 10 cases by MAZE surgical intervention) and 6 underwent cardiac repair for a congenital heart disease (4%, one tetralogy of Fallot, four atrial septal defect, one atrioventricular canal defect plus great vessel transposition). Baseline characteristics and procedural data are summarized in *Tables 1* and *2* respectively. A total of 281 flutters were targeted for ablation during the course of which 640 entrained sites were targeted by RFD. Of these, 95 entrainment sequences-sites were excluded; 72 based on the above criteria and 23 because post-pacing artefacts hampered the interpretation. Because of 2:1 atrioventricular conduction or noise, StP and EgmP could be measured only in 460/545 (84.4%) sites.

Entrainment results are summarized in *Table 3*. Overall, 247/545 (45.3%) entrainment sequence sites exhibited a dPPI < 0 and 298/545 (54.7%) a dPPI = 0–30 ms. Entrainment manoeuvres resulted in 169/460 (36.7%) StP < EgmP, 131/460 (28.5%) StP = EgmP, 160/460 (34.8%) StP > EtP. StP < EgmP was observed more frequently at sites with dPPI < 0 compared to dPPI = 0–30 ms (125/208 vs. 44/252; 60.1% vs. 17.5%; $P < 0.001$). Correlation was found between dPPI and dStP-EgmP (Pearson 0.52; $P < 0.001$).

dPPI < 0 was associated with concealed entrainment (dPPI < 0 vs. dPPI = 0–30 ms, 246/247 vs. 187/298; 99.6% vs. 62.8%; $P < 0.001$), electrogram fractionation (dPPI < 0 vs. dPPI = 0–30 ms, 177/247 vs. 179/298; 71.6% vs. 60.1%; $P = 0.005$), and use of 3D mapping (dPPI < 0 vs. dPPI = 0–30 ms, 221/247 vs. 245/298; 89.5% vs. 82.2%; $P = 0.017$), compared to dPPI = 0–30 ms.

Ablation outcomes

RFD results are summarized in *Table 3*. RFD resulted in flutter termination on 109/545 (20%) sites, TCL increase on 109/545 (20%) sites, change in the activation sequence on 22/545 (4%) sites; RFD caused no change in flutter characteristics on 290/545 sites (53.2%). At 15 sites (2.8%) pacing at high output during entrainment terminated the flutter, subsequent ablation was performed in sinus rhythm and the same arrhythmia was non-inducible.

RFD terminated flutter at 67/241 (27.8%) sites in the dPPI < 0 group vs. 42/289 (14.5%) in the dPPI = 0–30 group ($P < 0.001$). AFL termination was associated with a shorter dPPI duration (−5.67 ± 16.59 ms vs. 0.24 ± 13.96 ms; $P < 0.001$); with a logistic

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022

Table 2 Procedural findings

		177 procedures
Presenting arrhythmia, *N* (%)	Atypical flutter	126 (71.2%)
	Atrial fibrillation	82 (28.8%)
3D mapping, *N* (%)	None	23 (13%)
	3D mapping system	154 (87%)
Flutter chamber, *N* (%)	Left atrial	260/281 (92.5%)
	Right atrial	21/281 (7.5%)
Circuit morphology, *N* (%)	Dual-loop re-entry	13/281 (4.6%)
	Single-loop re-entry	268/281 (95.4%)
Flutter loop circuit, *N* (%)	Perimitral	29/294 (9.9%)
	Roof dependent	30/294 (10.2%)
	Surgical scar related	11/294 (3.7%)
		2 left atrial, 9 right atrial
	Peri-pulmonary vein ostium	63/294 (21.4%)
	Endo-epicardial coronary sinus connection	42/294 (14.3%)
	Intercaval	4/294 (1.4%)
	Not fully defined[a]	115/294 (39.1%)
Complete 3D activation mapping, *N* (%)		209/281 (74.4%)
Targeted areas	Mitral annulus	18/281 (6.4%)
	Anterior left atrium	45/281 (16%)
	Posterior left atrium	42/281 (14.9%)
	Roof left atrium	31/281 (11%)
	Septal left atrium	40/281 (14.2%)
	Mitral isthmus	18/281 (6.4%)
	Left auricle	26/281 (9.3%)
	Pulmonary vein ostia	52/281 (18.5%)
	Coronary sinus	61/281 (21.7%)
	Right atrium septal	11/281 (3.9%)
	Atriotomy scar	5/281 (1.8%)
	Caval veins	8/281 (2.8%)
Electrograms targeted for ablation, *N* (%)		
545 ablations	Diastolic	416 (73.6%)
	Fractionated	356 (65.3%)
	Systolic non-fractionated	51 (9.4%)
Isoelectric intervals, *N* (%) (253 flutter ECGs)		163 (64.4%)
Isoelectic interval duration (ms)		119.28 (±34.78)
Procedure success, *N* (%)		137/177 (77.4%)
Procedure duration (min)		200 (±45)
Radiofrequency time (min)		25 (±14)
Fluoroscopy time (min)		47 (±18)

[a]Re-entrant circuit not being fully defined did not exclude critical isthmus localization/definition.

regression, we estimated that probability of termination was reduced [odds ratio (OR) 0.974, 95% confidence interval (CI) 0.960–0.988, $P < 0.001$] for every 1 ms increase of dPPI (*Figure 4*). Similarly, for every 1 ms increase of StP–EgmP, we observed a reduced probability of flutter termination (OR 0.988; 95% CI 0.977–0.999; $P = 0.033$).

A composite outcome including flutter termination and TCL increase (Full + Partial success) occurred at 122/241 (50.6%) sites in the dPPI < 0 group vs. 96/289 (33.2%) sites in the dPPI = 0–30 ms group ($P < 0.001$); it was associated with a reduced dPPI (−4.48 ± 15.18 ms vs. 1.48 ± 13.88 ms; $P < 0.001$). The probability of full or partial success was also reduced (OR 0.972; 95% CI 0.960–0.984; $P < 0.001$) for every 1 ms increase of dPPI.

12-lead electrocardiogram analysis

In 253/281 AFL, the 12-lead ECG could be analysed for the presence of isoelectric intervals. 12-lead synchronous isoelectric intervals were identified in 163/253 flutter ECGs (64.4%) and were significantly associated with dPPI < 0 (171/227 vs. 145/260; 75.3% vs. 55.8%; $P < 0.001$).

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022

Table 3 **Entrainment and ablation results**

Entrainment characteristics		545 entrainment sequences	
Tachycardia cycle length (ms)		280.76 (±61.31)	
Pacing cycle length (ms)		260.90 (±58.52)	
Post-pacing interval (ms)		279.88 (±59.22)	
PPI-TCL (ms)		−0.88 (±14.60)	
Pacing pulses (*N*)		13.48 (±4.37)	
Stimulus-to-flutter 'p' wave (ms)		160.46 (±69.41)	
EGM-to-flutter 'p' wave (ms)		160.45 (±76.53)	
StP-Egmp (ms)		0.005 (±21.30)	
Concealed vs. manifest entrainment		(*P* < 0.001)	
	dPPI 0–30 ms (*N* = 298)	dPPI < 0 ms (*N* = 247)	Total (*N* = 545)
Concealed	187 (187/298; 62.8%)	246 (246/247; 99.6%)	433 (433/545; 79.4%)
Manifest	111 (111/298; 37.2%)	1 (1/247; 0.4%)	112 (112/545; 20.6%)
Stimulus-to-flutter 'p' wave–EGM-to-flutter 'p' wave		(460/545 manoeuvres; 84.4%)	
	Shorter + equal vs. longer	(*P* < 0.001)	
	Shorter vs. equal	(*P* < 0.001)	
	dPPI 0–30 ms (*N* = 252)	dPPI < 0 ms (*N* = 208)	Total (*N* = 460)
StP < EgmP	44 (44/252; 17.5%)	125 (125/208; 60.1%)	169 (169/460; 36.7%)
StP = EgmP	80 (80/252; 31.7%)	51 (51/208; 24.5%)	131 (131/460; 28.5%)
StP > EgmP	128 (128/252; 50.8%)	32 (32/208; 15.4%)	160 (160/460; 34.8%)
Targeted EGM vs. dPPI			(*P* = 0.131)
	dPPI 0–30 ms (*N* = 298)	dPPI < 0 ms (*N* = 247)	Total (*N* = 545)
Diastolic	220 (220/298; 73.8%)	196 (196/247; 79.4%)	416 (129/545; 76.3%)
Systolic	78 (78/298; 26.2%)	51 (51/247; 20.6%)	129 (129/545; 23.7%)
EGM morphology vs. dPPI			(*P* = 0.005)
	dPPI 0–30 ms (*N* = 298)	dPPI < 0 ms (*N* = 247)	Total (N = 545)
Fractionated	179 (179/298; 60.1%)	177 (177/247; 71.6%)	356
Non-fractionated	119 (119/298; 39.9%)	70 (70/247; 28.4%)	189
3D-mapping use vs. dPPI			(*P* = 0.017)
	dPPI 0–30 ms (*N* = 298)	dPPI < 0 ms (*N* = 247)	Total (*N* = 545)
3D mapping	245 (245/298; 82.2%)	221 (221/247; 89.5%)	466 (466/545; 85.5%)
No 3D mapping	53 (53/298; 17.8%)	26 (26/247; 10.5%)	79 (79/545; 14.5%)
Radiofrequency ablation results			530 ablation sites
	dPPI 0–30 ms (*N* = 289)	dPPI < 0 ms (*N* = 241)	Total (*N* = 530)
Flutter termination	42 (42/289; 14.5%)	67 (67/241; 27.8%)	109 (109/530; 20.6%)
Increased TCL	54 (54/289; 18.7%)	55 (55/241; 22.8%)	109 (109/530; 20.6%)
Activation sequence change	12 (12/289; 4.2%)	10 (10/241; 4.2%)	22 (22/530; 4.1%)
Unchanged	181 (181/289; 62.6%)	109 (109/241; 45.2%)	290 (290/530; 54.7%)
Flutter termination vs. no termination			(*P* < 0.001)
	dPPI 0–30 ms (*N* = 289)	dPPI < 0 ms (*N* = 241)	Total (*N* = 530)
Flutter termination	42 (42/289; 14.5%)	67 (67/241; 27.8%)	109 (109/530; 20.6%)
No termination	247 (247/289; 85.5%)	174 (174/241; 72.2%)	421 (421/530; 79.4%)
Full + partial success vs. no success			(*P* < 0.001)
	dPPI 0–30 ms (*N* = 289)	dPPI < 0 ms (*N* = 241)	Total (*N* = 530)
Full + partial success	96 (96/289; 33.2%)	122 (122/241; 50.6%)	218 (218/530; 41.1%)
No success	193 (193/289; 66.8%)	119 (119/241; 49.4%)	312 (312/530; 58.9%)

dPPI, post-pacing interval-tachycardia cyle length; EGM, electrogram; EgmP, EGM-to-'p' wave interval; PPI, post-pacing interval; StP, stimulus-to-'p' wave inteval; TCL, tachycardia cycle length.

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022

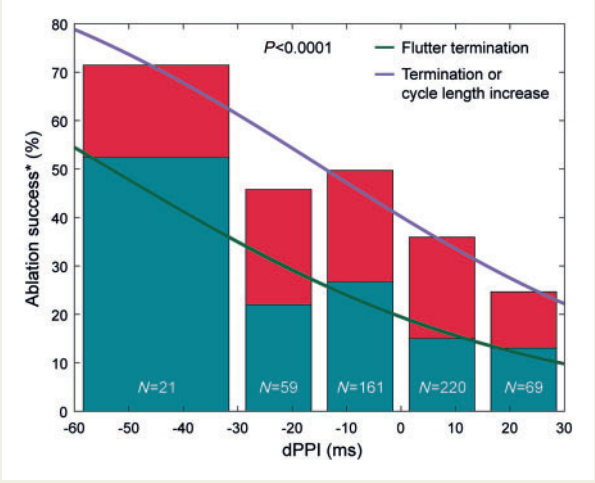

Figure 4 The logistic regression model shows the increasingly inverse correlation between circuit modification (increase in tachycardia cycle length > 20 ms + flutter termination-purple line) or flutter termination (green line) based on dPPI. The teal bars show probability of termination to sinus rhythm, red bars show probability of circuit modification.

A multivariate model was used to investigate dPPI association with demographic and clinical variables (*Table 4*). Factors independently associated with dPPI < 0 were the presence of isoelectric intervals on 12-lead ECG (OR 3.13; 95% CI 1.47–16.39; $P = 0.003$), StP < EgmP (OR 8.82; 95% CI 4.74–16.39; $P < 0.001$) and concealed entrainment (manifest entrainment predicted dPPI = 0–30 perfectly).

Discussion

The main finding of this study is that a combined strategy of activation and entrainment mapping provides a high degree of acute success in AFL ablation. In this large series of re-entrant AFL a strategy of preliminary widely separated biatrial entrainment (from large—up to 15 cm—coverage decapolar catheters) followed by 'precision' entrainment mapping at candidate sites, selected on the basis of activation mapping, revealed a 45.3% incidence of dPPI < 0 ms out of all dPPI values <30 ms. RFD at sites with dPPI < 0 ms resulted in higher rates of flutter termination compared to dPPI = 0–30 ms and a 51% probability of termination or TCL slowing vs. 33% for sites with dPPI = 0–30 ms. Therefore, negative dPPI values may indicate areas critical for the re-entry circuit with greater specificity than dPPI = 0–30 ms. This inference is reinforced by the continuous inverse relationship of flutter modification (termination or slowing)

Table 4 **Mixed-effects multivariate analysis**

	dPPI < 0 (*N* = 247)	dPPI = 0–30 (*N* = 298)	P univariate	P multivariable[c]
TCL (ms)	286.5 ± 59.3	276.0 ± 57.4	0.031[a]	0.4
Fractionated electrogram (*n*, %)	177 (71.7%)	179 (60.1%)	0.005	0.12
12-lead isoelectric interval (*n*, %)	171/227 (75.3%)	145/260 (55.8%)	0.00005[a]	0.003
Concealed entrainment (*n*, %)	246 (99.6%)	187 (62.8%)	<0.00001	Undefined[d]
Stim-to-'P'<EGM-to-'P' (*n*, %)	125/208 (60.1%)	44/252 (17.5%)	<0.00001	<0.00001
Age (years)	62.1 ± 11.3	60.9 ± 12.0	0.7[b]	0.4
BMI (kg/m^2)	28.0 ± 5.4	28.3 ± 5.4	0.7[b]	0.7
Male gender (*n*, %)	172 (69.6%)	222 (74.5%)	0.3[b]	0.5
Diabetes (*n*, %)	45 (18.2%)	37 (12.4%)	0.1[b]	0.4
Hypercholesterolaemia (*n*, %)	115 (46.6%)	142 (47.7%)	0.6[b]	0.8
Previous stroke/TIA (*n*, %)	21 (8.5%)	27 (9.1%)	0.8[b]	0.6
Hypertension (*n*, %)	119 (48.2%)	124 (41.6%)	0.5[b]	0.4
CHA_2DS_2-VASc ≥ 2 (*n*, %)	149 (60.3%)	156 (52.4%)	0.4[b]	0.4
Previous myocardial infarction (*n*, %)	44 (17.8%)	66 (22.2%)	0.2[b]	0.2
Current amiodarone therapy (*n*, %)	56 (22.7%)	59 (19.8%)	0.3[b]	0.2
Previous AF ablation (*n*, %)	176 (71.3%)	193 (64.8%)	0.2[b]	0.2
Previous heart surgery (*n*, %)	47 (19.0%)	64 (21.5%)	0.6[b]	1.0
LVEF < 50% (*n*, %)	85 (33.6%)	87 (29.8%)	0.6[b]	0.07
RA surface (cm^2)	20.2 ± 5.3	19.6 ± 5.2	0.4[b]	0.6
LA surface (cm^2)	25.1 ± 6.3	25.8 ± 6.3	0.2[b]	0.7

AF, atrial fibrillation; BMI, body mass index; dPPI, post-pacing interval-tachycardia cyle length; EGM, electrogram; LA, left atrium; LVEF, left ventricular ejection fraction; RA, right atrium; TCL, tachycardia cycle length; TIA, transient ischaemic attack.
[a]Mixed effects model to account for clustering by flutter. Reported means and standard deviations are indicative and do not account for clustering (the same flutter may be counted more than once).
[b]Mixed effects model to account for clustering by patient. Reported means and standard deviations are indicative and do not account for clustering (the same individual may be counted more than once).
[c]Mixed effects model to account for clustering by patient and by flutter.
[d]Manifest fusion predicted dPPI = 0–30 perfectly.

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022

with dPPI value, such that this probability increased with more negative dPPIs. Indeed, the OR of ablation success is 1.03 per 1 ms decrease in dPPI, such that a decrease in dPPI from 0 ms to −20 ms is associated with an absolute 10% increase in ablation full success.

A finding with a similar relationship is StP-EgmP < 0. While StP and EgmP intervals may be difficult to measure precisely and in a reproducible fashion during AFL ablation, these intervals may represent a useful surrogate for mappable re-entrant ventricular tachycardia ablation since stimulus to QRS interval and electrogram to QRS intervals can be measured more reliably from the surface ECG, particularly for noisy tracings and low voltage electrograms. The $N+1$ technique, may also be useful for evaluating the PPI in case of pacing electrode noise and might additionally reduce errors in comparing intervals to P/flutter waves due to varying fusion on the surface ECG.[14]

The high proportion of dPPI < 0 reported in this study can be explained by a strategy which integrates preliminary entrainment mapping with information derived from prior activation mapping, so that the final 'precision' entrainment manoeuvres were typically performed at 'good' candidate sites within the circuit. In addition, entrainment was performed repeatedly at neighbouring sites to identify precisely the site of shortest dPPI as well as to systematically evaluate sites with fractionated electrograms. Indeed, because of the large dimensions of the virtual electrode, a careful electrogram analysis and repeated measurements are fundamental to discriminate smaller components of the re-entrant circuit from the critical isthmus. Finally, a 25 mA pacing output was adopted to be sure that the underlying tissue was consistently stimulated; this high output may have resulted in a wider area of tissue capture, thereby increasing the probability of dPPI < 0 as explained below.[15] Nevertheless, entrainment manoeuvres subsequently performed at the same spot with an output lower than 25 mA confirmed our findings (*Figure 3*).

Mechanism of negative dPPIs

The interval between the last entrained pacing stimulus and the subsequent electrogram, the PPI, is a function of the distance between the pacing site and the re-entry circuit, but more specifically, of the intervening conduction velocity and distance. Many factors may alter normal myocardial conduction and atrial structure, but the underlying mechanism of negative dPPIs has not been systematically investigated until recently. Indeed, a negative dPPI is commonly considered an error caused by intermittent tissue capture or entrainment of a far field electrogram. These phenomena were excluded in our study by accurate offline electrogram analysis.

In our study, previous medical history and antiarrhythmic therapy showed no association with the occurrence of negative dPPI. The associated electrophysiological findings, notably the co-occurrence of concealed entrainment and StP timings not longer than and actually shorter than EgmP timings suggest a precise functional location—a protected zone of slow conduction—within the re-entry circuit or rarely, a dead-end bystander connected to the middle of this slow conduction zone (although in this case, the PPI is expected to be longer than the TCL, even if slightly). The frequent finding of a 12-lead synchronous isoelectric interval in this group supports this hypothesis, as does the frequent occurrence of flutter termination or TCL prolongation with a few RFDs. A recent ultra-high-density mapping study provided corroboratory findings suggesting that virtual electrode downstream direct capture within a restricted isthmus of slow conduction results in 'shortening' of the return circuit, with resulting PPIs shorter than the TCL.[15] The higher stimulation output used in our patients resulting in a larger virtual electrode likely potentiated the shortening of PPIs that was observed in this study.

Limitations

This study is subject to the constraints of a retrospective cohort analysis from a single centre, although this series represents one of the larger experiences of its kind. Entrainment manoeuvres were performed after activation mapping with high amplitude stimulation and preliminary entrainment mapping excluded sites far from the re-entry circuit, therefore the predictive accuracy of dPPI < 0 needs to be validated in a prospective study comparing conventional low output entrainment approaches.

Conclusion

A PPI shorter than TCL is a frequent finding in patients with AFL with a strategy combining activation and entrainment mapping. Sites with a PPI shorter than TCL represent highly effective targets for AFL ablation, providing better results compared to conventionally accepted PPI thresholds of 0–30 ms > TCL. In addition, PPI < TCL was significantly associated with 12 lead synchronous isoelectric intervals on surface ECG and StP < EgmP, which are markers of the presence of a narrow slow-conducting isthmus.

Funding

This work was supported by the Swiss National Science Foundation (173007 to D.C.S.); Department of Medicine Scholarship of the University Hospital of Geneva (to N.J.).

Conflict of interest: P.B.D.A.: none declared. N.J.: received educational grants from Boston Scientific, Abbott, Cardinal Health. M.N.: received consultant fees and travel grants from Boston Scientific, Biotronik and Biosense Webster. D.C.S.: received consultant fees from Biosense Webster and Boston Scientific. He has benefited from research and fellowship and travel grants from Biosense Webster, Boston Scientific, Abbott and Biotronik, via the Cardiology Division, Geneva University Hospitals.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Patel AM, d'Avila A, Neuzil P, Kim, Msee SJ, Mela T, Singh JP *et al.* Atrial tachycardia after ablation of persistent atrial fibrillation: identification of the critical isthmus with a combination of multielectrode activation mapping and targeted entrainment mapping. *Circ Arrhythm Electrophysiol* 2008;**1**:14–22.
2. Winkle RA, Moskovitz R, Mead RH, Engel G, Kong MH, Fleming W *et al.* Ablation of atypical atrial flutters using ultra high density-activation sequence mapping. *J Interv Card Electrophysiol* 2017;**48**:177–84.
3. Strisciuglio T, Vandersickel N, Lorenzo G, Van Nieuwenhuyse E, El Haddad M, De Pooter J *et al.* A. Prospective evaluation of entrainment mapping as an adjunct to new generations high-density activation mapping systems of left atrial tachycardias. *Heart Rhythm* 2020;**17**:211–9.
4. Delacretaz E, Ganz LI, Soejima K, Friedman PL, Walsh EP, Triedman JK *et al.* Multiple atrial macro-re-entry circuits in adults with repaired congenital heart

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022

disease: entrainment mapping combined with three-dimensional electroanatomic mapping. *J Am Coll Cardiol* 2001;**37**:1665–76.
5. Wazni OM, Saliba W, Fahmy T, Lakkireddy D, Thal S, Kanj M *et al.* Atrial arrhythmias after surgical maze: findings during catheter ablation. *J Am Coll Cardiol* 2006; **48**:1405–9.
6. Kalman JM, Olgin JE, Saxon LA, Lee RJ, Scheinman MM, Lesh MD. Electrocardiographic and electrophysiologic characterization of atypical atrial flutter in man: use of activation and entrainment mapping and implications for catheter ablation. *J Cardiovasc Electrophysiol* 1997;**8**:121–44.
7. Shah D, Sunthorn H, Burri H, Gentil-Baron P, Pruvot E, Schlaepfer J *et al.* Narrow, slow-conducting isthmus dependent left atrial reentry developing after ablation for atrial fibrillation: ECG characterization and elimination by focal RF ablation. *J Cardiovasc Electrophysiol* 2006;**17**:508–15.
8. Stevenson WG, Sager PT, Friedman PL. Entrainment techniques for mapping atrial and ventricular tachycardias. *J Cardiovasc Electrophysiol* 1995;**6**:201–16.
9. Santangeli P, Dixit S. Role of entrainment in the era of high-density activation mapping for characterizing the reentrant circuit. *Heart Rhythm* 2017;**14**:1550–1.
10. Deo R, Berger R. The clinical utility of entrainment pacing. *J Cardiovasc Electrophysiol* 2009;**20**:466–70.
11. Stevenson WG, Weiss JN, Wiener I, Nademanee K, Wohlgelernter D, Yeatman L *et al.* Resetting of ventricular tachycardia: implications for localizing the area of slow conduction. *J Am Coll Cardiol* 1988;**11**:522–9.
12. Tung R. Challenges and pitfalls of entrainment mapping of ventricular tachycardia. *Circ Arrhythmia Electrophysiol* 2017;**10**:1–11.
13. Jaïs P, Matsuo S, Knecht S, Weerasooriya R, Hocini M, Sacher F *et al.* A deductive mapping strategy for atrial tachycardia following atrial fibrillation ablation: importance of localized reentry. *J Cardiovasc Electrophysiol* 2009;**20**:480–91.
14. Soejima K, Stevenson WG, Maisel WH, Delacretaz H, Brunckhorst CB, Ellison KE *et al.* The N + 1 difference: a new measure for entrainment mapping. *J Am Coll Cardiol* 2001;**37**:1386–94.
15. Johner N, Shah DC, Jousset F, Dall'Aglio PB, Namdar M. Electrophysiological and anatomical correlates of sites with post-pacing intervals shorter than tachycardia cycle length in atypical atrial flutter. *Circ Arrhythm Electrophysiol* 2019;**12**: e006955.

Downloaded from https://academic.oup.com/europace/article/23/4/624/5983736 by University de Geneve user on 29 June 2022