Local impedance and ultra-high density 3-dimensional mapping results in improved ablation metrics for cavotricuspid isthmus dependent atrial flutter compared with conventional ablation and contact force-guided ablation with 3-dimensional mapping

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Abstract

Introduction - Multiple contact-based ablation technologies have been developed to allow real-time judgement of lesion effectiveness; local impedance (LI) guided ablation and the role of ultra-high density (UHD) mapping have not yet been evaluated for cavotricuspid isthmus dependent atrial flutter (CTI-AFL).

Methods - This non-randomised observational study evaluated patients undergoing CTI-AFL ablation using conventional, contact force (CF) and LI guided strategies. Ablation metrics were collected, and in the LI cohort, the use of UHD mapping for breakthrough was evaluated.

Results - 30 patients were included, 10 in each group. Mean total ablation time was significantly shorter with LI (3.2±1.3min) vs conventional (5.6±2.7min) and CF (5.7±2.0min, p=0.0042). Time from start of ablation to CTI block was numerically shorter with LI (14.2±8.0min) vs conventional and CF (19.7±14.1 and 22.5±19.1min, p=0.4408). There were no differences in the number of lesions required to achieve block, procedural success, complication rates or recurrence. 15/30 patients did not achieve block following first-pass ablation. UHD mapping rapidly identified breakthrough in the 5 LI patients, including epicardial-endocardial breakthrough (EEB) away from the line.

Conclusion - The use of LI for real-time assessment of lesion formation resulted in significantly less ablation requirement. UHD mapping rapidly identified breakthrough, including EEB, which would likely have been difficult to identify otherwise and possibly require extensive ablation, contributing towards shortening of time to CTI block with LI.

Key words - atrial flutter, cavotricuspid isthmus ablation, local impedance, ultra-high density mapping

Introduction

Cavotricuspid isthmus dependent atrial flutter (CTI-AFL), also known as typical atrial flutter, describes a macroreentrant circuit around the tricuspid valve annulus, with conduction through the CTI being a prerequisite for arrhythmia maintenance. The overall incidence in the general population is approximately 0.9%.[1] Radiofrequency (RF) catheter ablation of the CTI is the most effective treatment for this condition, with a single-procedure success rate of 95% and is a class I recommendation from the European Society of Cardiology.[2, 3] Ablation is performed along the CTI from the tricuspid annulus to the inferior vena cava (IVC) and successful outcome achieved when bi-directional conduction block is present across the ablation line. When this endpoint is met, recurrence rates are approximately 5%, with recurrence occurring when functional gaps are present within the ablation line, or when epicardial-endocardial breakthrough (EEB) occurs due to epicardial fibres bridging across the CTI.[2, 4, 5]

The conventional technique involves the use of bipolar intracardiac electrograms (EGMs), fluoroscopic image guidance and radiofrequency generator impedance to position catheters prior to applying RF. Due to the trabeculated and heterogeneous anatomy of the CTI it can be difficult to achieve a contiguous ablation line using only these metrics, resulting in extensive ablation and significant radiation exposure to both patient and operator.[4, 6]

Interest in optimising catheter-tissue contact and real-time metrics of effective ablation lesion delivery has resulted in the development of new technology to this end. A number of studies have evaluated contact force (CF, using the Thermocool SmartTouch ablation catheter; Biosense Webster, Diamond Bar CA, USA) or electrical coupling index (Ensite Verisense ECI ablation catheter; St Jude Medical, St Paul MN, USA) to improve assessment of catheter–tissue contact prior to RF energy delivery.[7-10] Recently, catheters that measure local tissue impedance (LI) have been developed (IntellaNav MiFi; Boston Scientific, Marlborough MA, USA) allowing measurement of tissue contact as well as a direct metric of lesion formation via drop in local impedance values. In vitro and in vivo studies have validated the use of LI as a valuable measure of catheter-tissue contact, and have also shown that a reduction in LI during application of RF to correspond to effective lesion formation.[11-13]

The use of adequate LI drop as an endpoint target for lesion formation may allow more effective and shorter lesion delivery when compared to other techniques. However, LI-guided ablation has not yet been evaluated against the routinely used conventional or contact force-guided ablation for CTI-AFL in humans. We hypothesised that information about baseline and LI drop would improve the time taken to create an effective lesion set by allowing real time assessment of lesion formation with consequent reduction in unnecessary duration of ablation.

Methods

This non-randomised observational pilot study compared patients undergoing RF ablation of CTI-AFL with fluoroscopic guided ablation (conventional group), CF-guided ablation with 3-dimensional (3D) electro-anatomic mapping (Carto-3, Biosense-Webster, CF group), and LI-guided ablation and ultra-high density (UHD) mapping

(Rhythmia HDx, Boston Scientific, LI group). Patients were eligible if they were aged greater than 18 years old undergoing first-time ablation of suspected CTI-AFL, either alone or as part of another ablation procedure. Those whose AFL was determined during the procedure to not be CTI dependent were excluded.

Procedures took place between 11th December 2018 and 5th October 2020 at a single tertiary cardiac centre by four experienced cardiac electrophysiologists familiar with all three technologies. Procedures were performed under local anaesthesia and conscious sedation or general anaesthetic. Intravascular access was obtained using left or right femoral veins as per operator preference. Oral anticoagulation (warfarin or direct oral anticoagulant) was continued peri-procedure. A decapolar catheter was inserted into the coronary sinus. The use of a right atrial 20-pole “halo” diagnostic catheter (Biosense Webster) for the conventional group or the creation of 3D right atrial anatomy and activation mapping (LI and CF groups) was left to the discretion of the operator. Steerable sheaths were used at operator discretion if satisfactory contact or stability could not be achieved.

A cavotricuspid isthmus line was created using a point by point approach. At each point irrigated RF energy was delivered for 30 seconds (conventional and CF groups) or until a target local impedance drop was achieved (LI group, see below). Bipolar electrogram reduction/elimination was aimed for in the conventional group. For all groups the power was limited to 40-50W depending on operator preference, with a maximum temperature of 48°C and flow of 30 ml/min as per manufacturer recommendations. The catheters used were; Thermocool (Biosense Webster) for the conventional group, Thermocool SmartTouch (Biosense Webster) for the CF group, and IntellaNav MiFi (Boston Scientific) for the LI group.

For the LI-guided group, contact was determined using patient-specific LI measurement by checking tissue contact LI against blood pool impedance, aiming for a starting contact impedance of 110-130 Ω. RF was applied until a maximum LI reduction of 20 Ω was achieved, or a plateau of at least 2 seconds was reached following an initial LI drop. If bi-directional CTI block was not obtained following first-pass ablation, additional lesions were delivered at breakthough gaps, with UHD mapping utilised at operator discretion to identify and characterise the nature of the breakthrough target for further ablation. For the CF-guided cohort a contact force of 9-40 grams was targeted for each lesion. If bi-directional CTI block was not obtained following first-pass ablation, additional lesions were delivered at breakthough gaps and 3D mapping could be performed at operator discretion to identify sites of breakthrough to target for further ablation.

Confirmation of bi-directional CTI block was obtained using standard multi-site pacing manoeuvres. Following confirmation of bi-directional block, an observation period of 30 minutes was carried out, in order to exclude recovery of conduction across the ablation line. Patients received clinically indicated follow up at 3, 6, and 12 months post-procedure, with a 12-lead ECG at the time of review to ensure maintenance of sinus rhythm, and further ambulatory ECG monitoring performed if symptoms suggestive of possible arrhythmia recurrence were reported.

Data collected included total RF time, time from first application of RF to confirmation of bi-directional CTI block, number of lesions required to achieve block, mean measurements for maximum, minimum and average CF per lesion (for CF-guided cases), and mean starting LI and LI drop (for LI-guided cases), acute procedural success, procedural complications and requirement for re-ablation during follow-up period. Analysis was performed using ANOVA for parametric data, with multiple comparisons ANOVA between groups corrected using the two-stage step-up method, or the Kruskal-Wallis test for non-parametric data. The chi-square or Fisher exact test was used for categorical variables. All statistical analysis was performed using Prism version 9.0 (GraphPad Software, San Diego CA, USA).

In cases where bi-directional block was not achieved following first-pass ablation, to allow analysis of breakthrough, division of the CTI into three segments was required - adjacent to the tricuspid valve annulus (TV-CTI), the mid-portion (mid-CTI) and adjacent to the inferior vena cava (IVC-CTI). Breakthrough points were grouped according to their location within these segments.

Results

Baseline characteristics

30 consecutive patients were included – ten in each of the three groups – conventional, contact force- and local impedance-guided ablation. There were no significant differences between the three groups in terms of age or the prevalence of common cardiovascular co-morbidities (Table 1), and there was a significant male

preponderance overall (86.7%). All patients who underwent conventional ablation had CTI ablation only, whilst five of ten patients who underwent CF-guided and one of ten patients undergoing LI-guided ablation had CTI ablation as part of a procedure in which they also underwent left atrial ablation for atrial fibrillation (AF).

Outcome measures

The mean total ablation time (cumulative time that RF was applied throughout the procedure) was 5.6 ± 2.7 minutes for conventional, 5.7 ± 2.0 minutes for CF-guided and 3.2 ± 1.3 minutes for LI-guided ablation (p=0.0042). Statistically significant differences were also seen individually between LI and conventional (p=0.0058) and between LI and CF groups (p=0.0031; Figure 1A). The mean time taken from first application of RF to confirmation of bi-directional CTI block (the time at which the final lesion was delivered prior to confirmation of block) was 19.7 ± 14.1 min for conventional, 22.5 ± 19.1 min for CF and 14.2 ± 8.0 min for LI-guided ablation (p=0.4408; Figure 1B). The number of lesions required to achieve block was 9.2 ± 3.5 for conventional, 12.6 ± 6.5 for CF-guided and 8.0 ± 2.5 for LI-guided groups (p=0.0769; Figure 1C). Mean CF measurement was 15.3g ± 3.6g for CF-guided cases, with a mean maximum CF value of 24.5g ± 5.5g and mean minimum CF value of 9.2g ± 2.0g. Mean starting LI was 112.7 ± 13.6 Ω and mean LI drop 21.2 ± 7.8 Ω for LI-guided cases. There was 100% acute procedural success, no reported procedural complications and no requirement for repeat ablation during the follow-up period for all three groups (14.6 ± 8.5 months for conventional, 15.1 ± 8.8 months for CF and 9.9 ± 4.6 months for LI; p=0.2394).

Sites of acute breakthrough

First-pass bi-directional block was not achieved in four conventional, six CF and five LI patients (p=0.6703). In the LI-guided group these five patients underwent UHD mapping of the CTI to identify the precise location and nature of breakthrough (Figure 2). The mean length of the CTI was 35.2 ± 2.8 mm. Four patients had linear breakthrough at the CTI; one patient 4.2mm from the tricuspid valve annulus (TV-CTI segment, Figure 3), and three between 20.2 and 29.8mm from the TV annulus (IVC-CTI segment). In one patient the breakthrough was away from the ablation line, 10.4mm lateral to the mid-CTI, representing epicardial-endocardial breakthrough (EEB; figure 4A and 4B).

Discussion

Ablation using contact force-sensing catheters has been validated as a robust way to assess the catheter-tissue interface and deliver lesions with lower rates of dormant conduction and electrical reconnection than catheters lacking this information.[8-10, 14, 15] The Thermocool SmartTouch catheter (Biosense Webster), used in this study uses data transmitted from a spring coil at the catheter tip, providing a direct measurement of the force applied by the catheter on the endocardium (displayed as grams), but does not measure tissue viability. The Ensite Verisense ECI catheter (St Jude Medical) aims to provide information on the viability of tissue by measuring tissue coupling by calculating ‘complex impedance’ derived from catheter measured tissue resistance and reactance. A reduction from baseline ECI of ≥12% reliably demonstrates loss of viability through transmural lesion formation in animal models, and higher rates of pulmonary vein isolation are seen with ECI-guided versus non-ECI guided RF ablation in humans (58% vs 30%).[16, 17] The VERISMART study recently evaluated ECI- versus CF-guided ablation for CTI-AFL found a reduced time from the start of ablation to confirmation of bi-directional block from 30.0 min to 10.5 min, demonstrating that the use of physiological tissue parameters may offer benefits over technologies measuring CF alone.[7]

The IntellaNav MiFi catheter (Boston Scientfic) uses a local potential field generated by three miniature electrodes at the catheter tip to measure local resistivity and therefore local impedance, rather than generator impedance used in other systems. Healthy tissue displays greater resistivity and LI (110 ± 13.7 Ω) than the surrounding blood pool (91.9 ± 9.9 Ω) hence providing the operator with some semi-quantitative information about catheter-tissue contact, with a plateau in high-impedance before reaching unsafe levels of contact force. An ex vivo study evaluating LI and CF showed 141-144 Ω to be equivalent to 31.5g (IQR 27-52g) of contact force.[11, 12] A patient-specific baseline local impedance for healthy tissue and blood pool are observed prior to RF application, for tissue by placing the catheter against the endocardium in multiple locations, with stability judged by tactile feedback, local electrograms and voltage, and for blood pool by placing the catheter in a cardiac chamber and confirming an absence of electrograms recorded by the catheter. A reduction from an baseline LI during RF application has been validated as an accurate measure of resistive heating and formation of transmural lesions.[12, 18] Clinical studies in the human left atrium and both ventricles have shown successful lesions to be correlated with a mean LI drop of 14.6 Ω and 16-18 Ω respectively.[11, 13]

This study evaluated the use of LI-guided ablation versus the conventional fluoroscopic and CF-guided ablation of CTI-AFL. The CTI has little anatomical variation between patients, the procedure involves relatively simple linear ablation and this therefore allows for the evaluation of the respective technologies in creating effective lesion sets whilst minimising confounding from underlying variability in substrate. This is supported by the fact that there was no significant difference in the number of lesions required to achieve bi-directional block across the three groups.

Ablation metrics

Total radiofrequency ablation time in the LI cohort was significantly reduced compared to the other two groups (p=0.0042). These differences were also individually statistically significant, with a 43% reduction versus conventional (p=0.0058) and 44% reduction versus CF (p=0.0031). This shorter duration suggests that on the CTI, effective lesion formation guided by LI drop allows a reduction in RF time without a reduction in acute success. Further corroboration of this can be observed by the fact that there was no significant difference between the groups in the total number of ablation lesions, suggesting that RF delivery guided by LI change during lesion formation shortens the required duration of each lesion. The operator is able to stop ablating once a significant LI drop has been observed and move onto creating the next lesion, rather than continue with each lesion for a pre-specified time, as with the conventional and CF-guided methods which offer no validated, real-time information on lesion formation. This benefit was maintained against good force in the CF group, as mean CF measurement during CF-guided ablation was 15.3g (± 3.6g), reflecting good catheter-tissue contact.

There was a reduction in time from first application of RF to confirmation of bi-directional CTI block using LI-guided ablation (14.2 ± 8.0 min) compared with conventional (19.7 ± 14.1 min) and CF groups (22.5 ± 19.1 min). Although statistically non-significant (p=0.4408), the reduction by 27.9% and 36.9% respectively in this suggestive that the use of LI guided ablation might be able reduce procedure time to CTI block when studied in a larger cohort. The VERISMART study that also used real time physiological ablation showed a significant reduction in time to bi-directional block with ECI versus CF-guided ablation. There were no differences between rates of complication or procedural success, defined by patient reported symptoms and 12-lead ECG performed at the time of follow-up.

CF and LI sensing catheters measure the catheter-tissue interface in different ways. The baseline LI measurement can give the operator some idea about tissue contact, as the blood pool displays lower impedance than the endocardium (91.9 ± 9.9 Ω for blood pool versus 110 ± 13.7 Ω for endocardium from a previous study, with mean baseline LI of endocardium in our analysis of 112.7 ± 13.6 Ω), although does not provide absolute force measurements like CF catheters. Real-time LI data during ablation reduces lesion duration and total RF time, whilst ablation with CF catheters does not have a validated method to guide RF delivery on the CTI. It could be postulated that less ablation associated with LI catheter use could reduce associated risk of complications, such as cardiac perforation and steam pops, though this study was not powered to assess these outcomes.

Analysis of breakthrough

First pass bi-directional isthmus block was not achieved in four conventional, six CF and five LI patients. In this study, UHD mapping was used to identify sites of breakthrough in the LI cohort when required. Figure 3 shows a UHD map of one case with breakthrough across the CTI. A single further ablation lesion at this point resulted in bi-directional CTI block. In another case, breakthrough was identified 10.4mm lateral to the CTI ablation line, with activation mapping showing outward radial spread from this point, with a unipolar rS pattern seen at the point of breakthrough, and identical activation timing on each pacing cycle length, representing epicardial-endocardial breakthrough. Further ablation at the point of the breakthrough resulted in bi-directional isthmus block in this patient (Figure 4). Studies utilising 3D mapping (Carto-3, Biosense Webster) have shown significant reduction in radiation use compared with conventional ablation for CTI-AFL, but not overall procedure time.[6, 19] Given the advantages of UHD mapping over standard electroanatomic mapping, the numerical reduction in time to CTI block, and rapid identification of breakthrough, it is possible a reduction in procedure time could be observed in a larger prospective trial.

Histological analysis of the CTI has shown it to be heterogeneous in its anatomy, receiving muscle fibres from the crista terminalis of varying number and morphology, separated by connective tissue. The TV segment is smooth, the mid-CTI is the most trabeculated, owing to the extensions of the pectinate muscles, and the IVC segment consists of fibro-fatty tissue.[20, 21] It could be postulated that breakthrough is most likely to occur in the mid-CTI as trabeculation can increase the difficulty of obtaining contact and transmural ablation. However in this study, three of four linear breakthrough points occurred at the IVC-CTI, with the other at the TV-CTI. The presence of a prominent Eustachian ridge or pouch in the IVC-CTI may cause difficulties in achieving effective ablation, and this may have accounted for breakthrough in these patients. In some cases, ablation lateral or medial to areas of breakthrough may be required if the underlying anatomy makes it difficult to achieve a contiguous lesion set.[22] In the LI cases, further ablation at the points of breakthrough identified by UHD mapping resulted in bi-directional block, but it is possible that in the other two groups without the aid of mapping, some variation in the plane of ablation line was adopted (medial or lateral to the first-pass line) in order to achieve block.

Intraoperative mapping studies have shown that EEB can be critical to the maintenance of human persistent AF.[23, 24] The development of UHD mapping provides an opportunity to study atrial endocardial activation patterns to a level of detail not previously possible. One study by Pathik *et al* observed and confirmed the presence of EEB in 14/26 patients undergoing ablation for CTI-AFL.[5] In all cases, EEB was present adjacent to a line of block, either occurring naturally in the RA (mostly in the posterior RA adjacent to the posterior line of block) during stable macroreentry, or near a successfully ablated CTI, and in a number of cases was a critical feature of the tachycardia. Sites of breakthrough were 13.4-19.4mm from the adjacent lines of block; in the case of EEB occurring medial to the CTI during counter-clockwise macroreentrant flutter, a single application of RF at this site resulted in termination of tachycardia. The case of EEB in this study was located 10.4mm lateral to the mid-CTI and to our knowledge, the first case of EEB uncovered during coronary sinus pacing.

The heterogenous muscle bundle arrangement at the CTI may contribute to the differential activation between epi- and endocardium and the formation of EEB within the vicinity of the CTI; in cases where epicardial fibres bridge the CTI, EEB may only be exposed following ablation creating a line of block.

Whilst there have been no studies systematically looking at EEB as a potentially significant factor in failure to achieve CTI block, its description in case reports, the regularity with which Pathik et al observed this phenomenon using UHD mapping, and its association with lines of block, it is possible that with further investigation it may be more frequently implicated in cases of treatment failure. The use of UHD mapping to identify and focus ablation at these sites may need to be considered if repeat procedures are planned.[5, 25, 26]

Conclusion

This pilot study shows statistically significant differences in total ablation time and a large numerical difference in time to bi-directional CTI block (although statistically non-significant due to large standard error) favouring LI-guided ablation. UHD mapping was seen to rapidly identify sites of breakthrough following the first-pass ablation line, which was unsuccessful in 15/30 patients, and this may have contributed towards the reduced ablation time for the LI cohort. A larger multi-centre prospective randomised study with appropriate power is planned.

Table and Figures [high resolution TIFF images available separately]

	Conventional n=10	CF-guided n=10	LI-guided n=10	p value
Age (SD)	69.7 (6.2)	61.3 (8.6)	66.0 (11.1)	p = 0.123
Male gender (%)	10 (100)	9 (90)	7 (70)	p = 0.133
Co-existing AF (%)	4 (40)	6 (60)	5 (50)	p = 0.670
Diabetes mellitus (%)	2 (20)	2 (20)	1 (10)	p = 0.787
IHD (%)	3 (30)	4 (40)	1 (10)	p = 0.303
HTN (%)	2 (20)	1 (10)	2 (20)	p = 0.787
LVSD (%)	4 (40)	5 (50)	4 (40)	p = 0.873

Table 1. Baseline characteristics.

AF, atrial fibrillation; IHD, ischaemic heart disease; HTN, hypertension; LVSD, left ventricular systolic dysfunction; SD, standard deviation

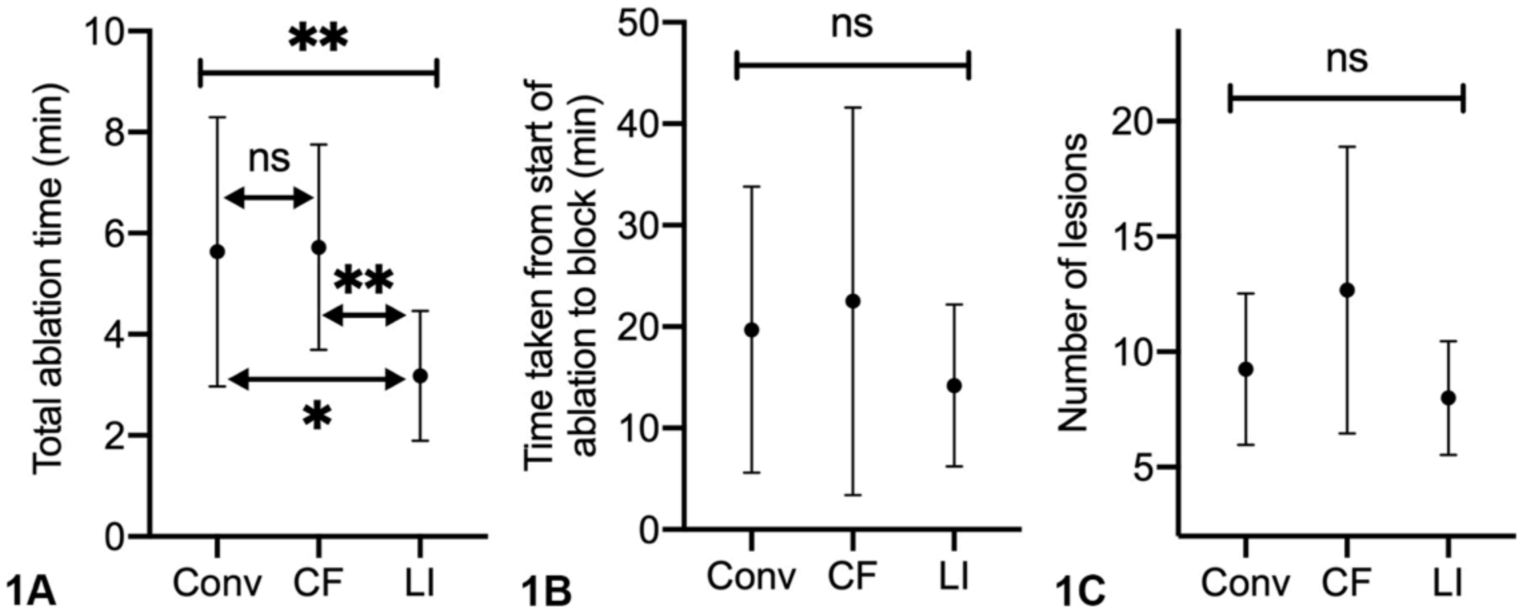

Figure 1. Graphs of ablation metric outcomes

1A. Total radiofrequency ablation time. 1B. Time taken from first application of radiofrequency ablation to confirmation of bi-directional cavotricuspid isthmus block. 1C. Number of lesions required to achieve bi-directional block. Dots and bars represent mean and standard deviation respectively.

* = $p<0.05$, ** = $p<0.005$, ns = non-significant ($p>0.05$)

Conv, conventional; CF, contact force; LI, local impedance

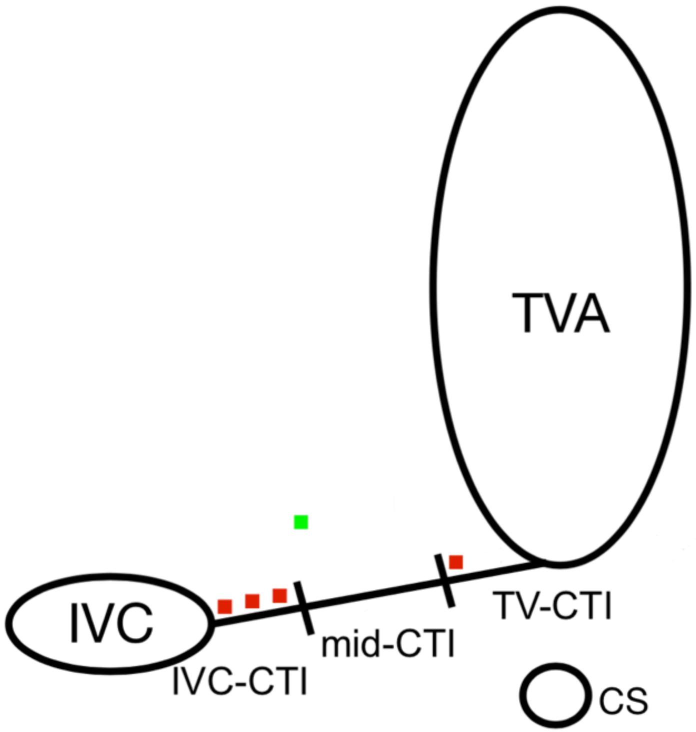

Figure 2. Simplified diagram of the cavotricuspid isthmus showing sites of breakthrough following first-pass ablation

The isthmus has been divided into three segments, based on proximity to TV, IVC or the mid-portion. Red points represent breakthrough across the line, green point shows epicardial-endocardial breakthrough lateral to line

TVA, tricuspid valve annulus; IVC, inferior vena cava; CS, coronary sinus ostium; CTI, cavotricuspid isthmus

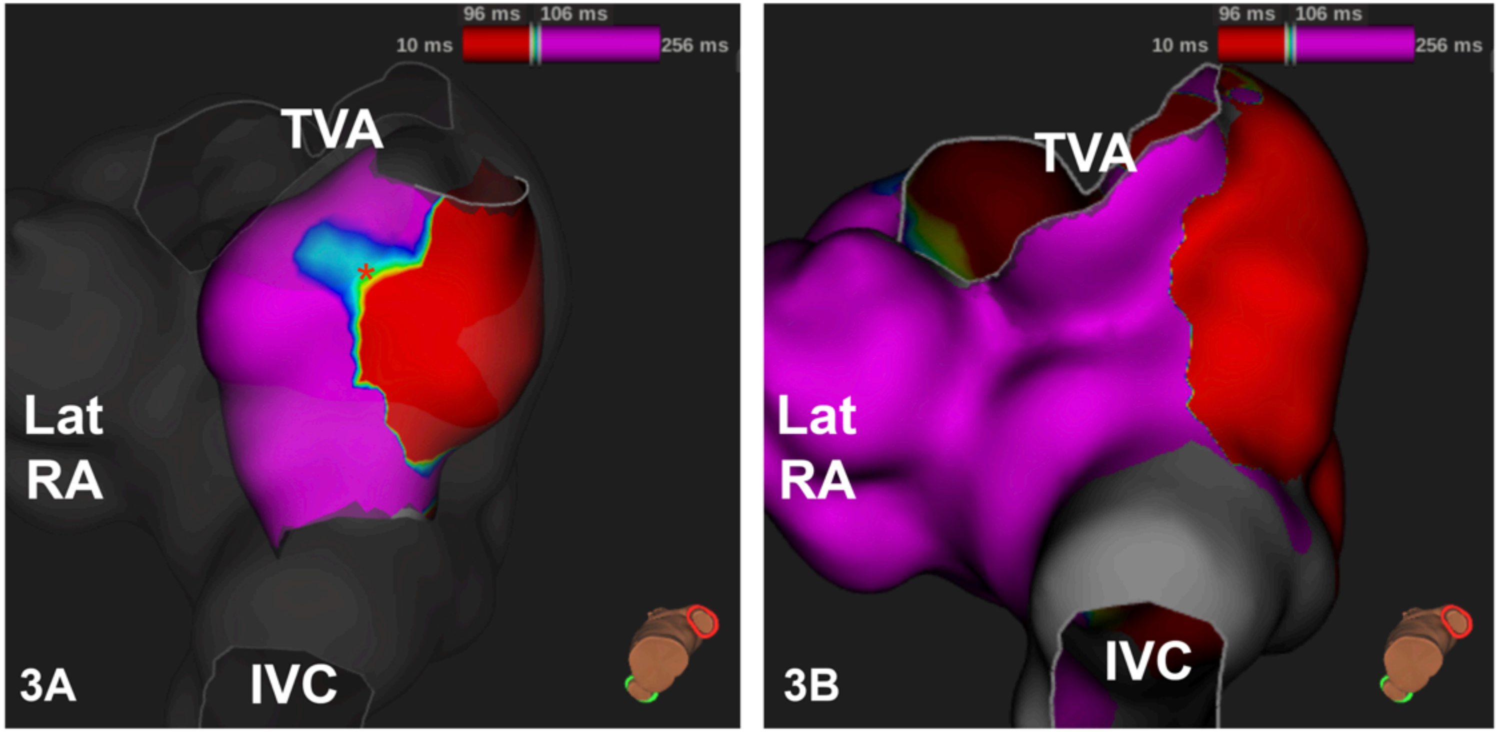

Figure 3. Ultra-high density 3-dimensional electroanatomic right atrial maps of the cavotricuspid isthmus (CTI) ablation line in a patient from the local impedance cohort, in left anterior oblique caudal view.

There is breakthrough across the tricuspid aspect of the ablation line (3A, red asterisk). Targeted ablation at this point resulted in bi-directional CTI block as shown in 3B. Timing is shown from the pacing electrode in the proximal coronary sinus and is displayed at the same timing in both maps; the activation wavefront is between 96ms and 106ms after pacing.

TVA, tricuspid valve annulus; IVC, inferior vena cava; Lat RA, lateral right atrium

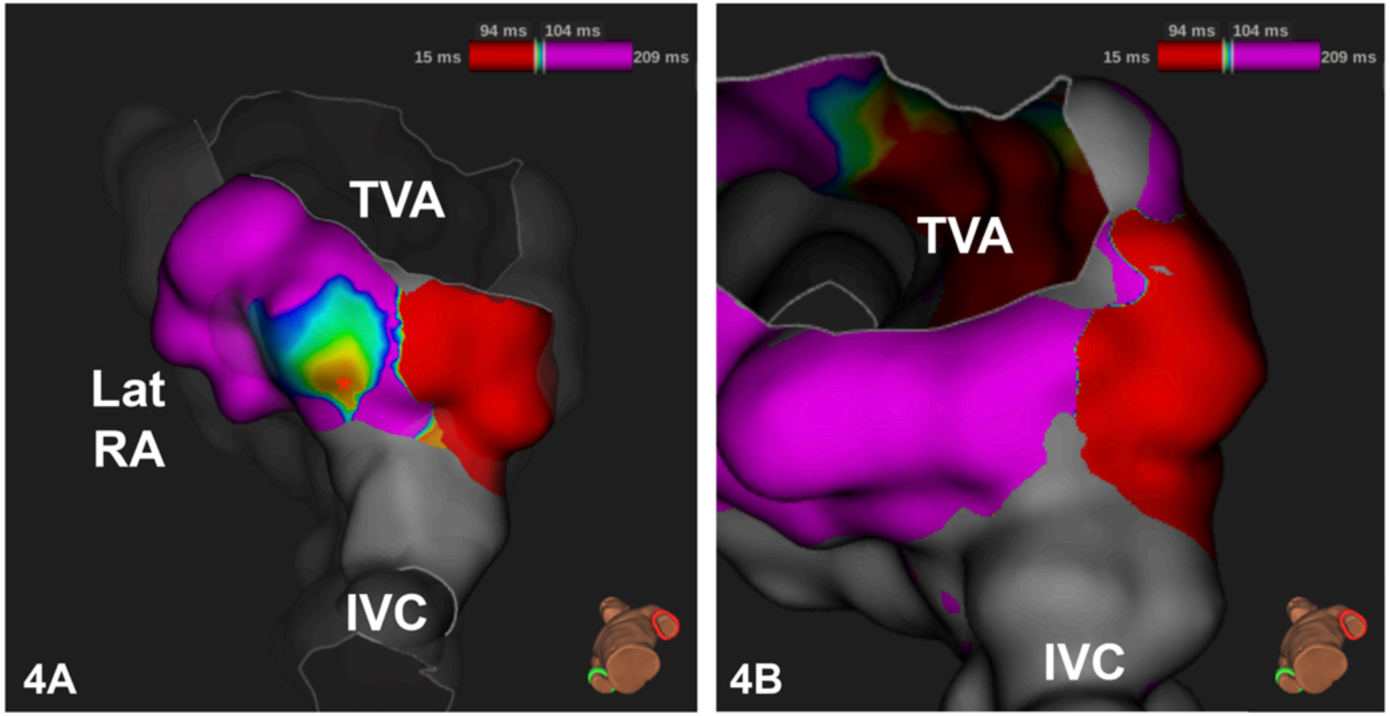

Figure 4. Ultra-high density 3-dimensional electroanatomic right atrial maps of the cavotricuspid isthmus (CTI) ablation line in a patient from the local impedance cohort, in left anterior oblique caudal view.

There is epicardial-endocardial breakthrough 10.4mm lateral to the cavotricuspid isthmus (CTI) ablation line, displaying radial spread (4A, red asterisk). Targeted ablation at this point resulted in bi-directional CTI conduction block as shown in 4B. Timing is shown from the pacing electrode in the coronary sinus and is displayed at the same timing in both maps; the activation wavefront is between 94ms and 104ms after pacing.

TVA, tricuspid valve annulus; IVC, inferior vena cava; Lat RA, lateral right atrium

References

1. Kircher S, Rolf S, Hindricks G, Sommer P. Ablation of typical atrial flutter using a novel non-fluoroscopic electromagnetic catheter tracking system. Interv Cardiol. 2014;6(2):1-10.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893-962.
3. Natale A, Newby KH, Pisano E, Leonelli F, Fanelli R, Potenza D, et al. Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. J Am Coll Cardiol. 2000;35:1898-904.
4. Willems S, Weiss C, Ventura R, Ruppel R, Risius T, Hoffman M, et al. Catheter Ablation of Atrial Flutter Guided by Electroanatomic Mapping (CARTO): A Randomized Comparison to the Conventional Approach. J Cardiovasc Electrophysiol. 2000;11(11):1223-30.
5. Pathik B, Lee G, Sacher F, Haissaguerre M, Jais P, Massoullie G, et al. Epicardial-endocardial breakthrough during stable atrial macroreentry: Evidence from ultra-high-resolution 3-dimensional mapping. Heart Rhythm. 2017;14(8):1200-7.
6. Kottkamp H, Hugl B, Krauss B, Wetzel U, Fleck A, Schuler G, et al. Electromagnetic versus fluoroscopic mapping of the inferior isthmus for ablation of typical atrial flutter: A prospective randomised study. Circulation. 2000;102:2082-6.
7. Begg GA, O'Neill J, Sohaib A, McLean A, Pepper CB, Graham LN, et al. Multicentre randomised trial comparing contact force with electrical coupling index in atrial flutter ablation (VERISMART trial). PLoS One. 2019;14(4):e0212903.
8. Haldar S, Jarman JW, Panikker S, Jones DG, Salukhe T, Gupta D, et al. Contact force sensing technology identifies sites of inadequate contact and reduces acute pulmonary vein reconnection: a prospective case control study. Int J Cardiol. 2013;168(2):1160-6.
9. Neuzil P, Reddy VY, Kautzner J, Petru J, Wichterle D, Shah D, et al. Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study. Circ Arrhythm Electrophysiol. 2013;6(2):327-33.
10. Kuck KH, Reddy VY, Schmidt B, Natale A, Neuzil P, Saoudi N, et al. A novel radiofrequency ablation catheter using contact force sensing: Toccata study. Heart Rhythm. 2012;9(1):18-23.
11. Munkler P, Gunawardene MA, Jungen C, Klatt N, Schwarzl JM, Akbulak RO, et al. Local impedance guides catheter ablation in patients with ventricular tachycardia. J Cardiovasc Electrophysiol. 2020;31(1):61-9.
12. Sulkin MS, Laughner JI, Hilbert S, Kapa S, Kosiuk J, Younan P, et al. Novel Measure of Local Impedance Predicts Catheter-Tissue Contact and Lesion Formation. Circ Arrhythm Electrophysiol. 2018;11(4):e005831.
13. Martin CA, Martin R, Gajendragadkar PR, Maury P, Takigawa M, Cheniti G, et al. First clinical use of novel ablation catheter incorporating local impedance data. J Cardiovasc Electrophysiol. 2018;29(9):1197-206.
14. Andrade JG, Monir G, Pollak SJ, Khairy P, Dubuc M, Roy D, et al. Pulmonary vein isolation using "contact force" ablation: the effect on dormant conduction and long-term

freedom from recurrent atrial fibrillation--a prospective study. Heart Rhythm. 2014;11(11):1919-24.
15. Shurrab M, Di Biase L, Briceno DF, Kaoutskaia A, Haj-Yahia S, Newman D, et al. Impact of Contact Force Technology on Atrial Fibrillation Ablation: A Meta-Analysis. J Am Heart Assoc. 2015;4(9):e002476.
16. Holmes D, Fish JM, Byrd IA, Dando JD, Fowler SJ, Cao H, et al. Contact sensing provides a highly accurate means to titrate radiofrequency ablation lesion depth. J Cardiovasc Electrophysiol. 2011;22(6):684-90.
17. Gaspar T, Sih H, Hindricks G, Eitel C, Sommer P, Kircher S, et al. Use of electrical coupling information in AF catheter ablation: a prospective randomized pilot study. Heart Rhythm. 2013;10(2):176-81.
18. Gunawardene M, Munkler P, Eickholt C, Akbulak RO, Jularic M, Klatt N, et al. A novel assessment of local impedance during catheter ablation: initial experience in humans comparing local and generator measurements. Europace. 2019;21(Supplement_1):i34-i42.
19. Hindricks G, Willems S, Kautzner J, De Chillou C, Wiedemann M, Schepel S, et al. Effect of electroanatomically guided versus conventional catheter ablation of typical atrial flutter on the fluoroscopy time and resource use: a prospective randomized multicenter study. J Cardiovasc Electrophysiol. 2009;20(7):734-40.
20. Ho S. Atrial structure and fibres: morphologic bases of atrial conduction. Cardiovascular Research. 2002;54(2):325-36.
21. Cabrera JA, Sanchez-Quintana D, Farre J, Rubio JM, Ho SY. The inferior right atrial isthmus: further architectural insights for current and coming ablation technologies. J Cardiovasc Electrophysiol. 2005;16(4):402-8.
22. Christopoulos G, Siontis KC, Kucuk U, Asirvatham SJ. Cavotricuspid isthmus ablation for atrial flutter: Anatomic challenges and troubleshooting. HeartRhythm Case Rep. 2020;6(3):115-20.
23. de Groot N, van der Does L, Yaksh A, Lanters E, Teuwen C, Knops P, et al. Direct Proof of Endo-Epicardial Asynchrony of the Atrial Wall During Atrial Fibrillation in Humans. Circ Arrhythm Electrophysiol. 2016;9(5).
24. de Groot NM, Houben RP, Smeets JL, Boersma E, Schotten U, Schalij MJ, et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. Circulation. 2010;122(17):1674-82.
25. Saraf K, Ariyaratnam J, Zaki A, Morris GM. Lateral epicardial breakthrough as a perpetuator of cavotricuspid isthmus conduction despite bidirectional mid-isthmus block: an important diagnostic role for high-density electroanatomical mapping. EP Europace. 2018;20(S1):i96.
26. Higuchi S, Shoda M, Iwanami Y, Yagishita D, Ejima K, Hagiwara N. Targeting an epicardial-endocardial breakthrough in a case with an intractable common atrial flutter using ultra-high-resolution three-dimensional mapping. Pacing Clin Electrophysiol. 2018;41(9):1261-3.