Association of coronary sinus activation differences with atrial remodeling in atrial fibrillation

Iskander Huijsse, Ben J M Hermans, Stef Zeemering, Dominik Linz, Ulrich Schotten

[1]Department of Physiology, Maastricht University,, The Netherlands

Abstract

Atrial fibrillation (AF) recurrence after pulmonary vein isolation remains common, and markers of atrial remodelling obtainable from routinely recorded data would be clinically valuable. A decapolar catheter is routinely positioned in the coronary sinus (CS) during ablation; we investigated whether interelectrode activation time differences (ΔT) between neighbouring electrode pairs reflect AF phenotype or left atrial dilatation.

CS recordings from 343 patients undergoing first-time ablation in sinus rhythm were drawn from two prospective cohorts (ISOLATION 1 and 2). After quality screening, 124 patients remained (92 paroxysmal, 32 persistent). Local activation times were determined per bipolar lead; ΔT was defined as the absolute difference between neighbouring pairs and summarised as the median per patient.

ΔT was narrowly distributed (median 10 ms, IQR 9–11 ms), with no difference between AF phenotypes ($p = 0.538$) and no correlation with left atrial volume index ($R = 0.073$, $p = 0.463$).

CS interelectrode activation time differences were unrelated to AF phenotype or left atrial dilatation, likely constrained by the 1 kHz temporal resolution relative to the 10 mm electrode spacing.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia [1] and is associated with progressive structural and electrical atrial remodelling [2]. Pulmonary vein isolation (PVI) is the cornerstone of catheter ablation for AF [1], yet recurrence after a single procedure remains common [3]. AF phenotype (paroxysmal vs. persistent) and left atrial dilatation, quantified by the left atrial volume index (LAVI), are recognised predictors of recurrence after PVI [3]. Both result from progressive atrial remodelling, but neither directly characterises the underlying electrophysiological substrate. Additional electrophysiological insight into atrial remodelling is therefore warranted and may help improve stratification of the atrial substrate, ultimately supporting better AF management.

Atrial remodelling can alter atrial conduction, resulting in slower and more heterogeneous propagation through the substrate [2]. This may manifest as prolonged atrial activation times, a recognised marker of atrial remodelling [4]. A decapolar mapping catheter is routinely positioned in the coronary sinus (CS) during AF ablation, providing electrograms that may reflect the underlying atrial substrate. Prolonged conduction time between the high right atrium and the CS is associated with AF recurrence after ablation [5,6], and CS-derived conduction intervals have been shown to distinguish patients at higher risk of AF onset and recurrence [7]. A longer interelectrode activation time difference between neighbouring CS electrode pairs may likewise reflect more advanced atrial remodelling. Establishing such an association could provide a readily available marker of atrial remodelling without requiring changes to the current ablation workflow, as it would rely on electrogram data that are already routinely recorded.

We hypothesised that longer CS interelectrode activation time intervals are associated with more advanced atrial remodelling. We therefore retrospectively assessed CS electrogram recordings available within the prospective ISOLATION 1 and 2 cohorts [8]. We first characterised the distribution of these intervals and then examined their association with AF type and LAVI.

2. Methods

2.1. Study population

Patients were drawn from two prospective cohorts conducted at Maastricht University Medical Center: the completed ISOLATION study (NCT04342312) and the ongoing ISOLATION 2.0 study (NCT05381805). Patients were eligible if they underwent a first-time AF ablation and were in sinus rhythm (SR) at the start of the procedure. The CS recordings of eligible patients were subsequently screened for signal quality (Section 2.3).

The ISOLATION study protocol has been described previously [8]. The study adhered to the principles of the Helsinki Declaration and was reviewed and approved by the local ethical committee (METC azM/UM). ISOLATION was approved under NL70787.068.19; ISOLATION 2.0 was approved under NL80761.068.22. All patients were 18 years or older and provided written

informed consent.

2.2. Signal acquisition and pre-processing

Twelve-lead surface ECG and CS electrograms were acquired continuously throughout the procedure using the Boston Scientific Lab System Pro Recording System (1000 Hz sampling frequency, 16-bit resolution; bandpass filter 0.1–25 Hz for ECG, 30–250 Hz for CS electrograms). CS electrograms were recorded with a decapolar catheter (Biosense Webster, 2 mm electrode tip, 2-8-2 mm interelectrode spacing), yielding five bipolar leads. For each patient, a 10-minute segment displaying stable atrial activity with minimal periods of pacing was manually selected at the time of export, from the interval between the start of CS recording and delivery of the first ablation lesion (cryoablation, radiofrequency ablation or pulsed-field ablation). All recordings were exported and analysed offline using MATLAB [10].

2.3. Recording quality screening

CS recordings were screened for eligibility before automated analysis. A segment was considered eligible if it contained at least one usable portion in which atrial deflections were present on at least two neighbouring bipolar leads and activation spread from proximal (CS9-10) to distal (CS1-2) in the majority of beats, consistent with sinus rhythm. Screening was performed by a single observer (IH), blinded to AF type and LAVI.

2.4. ECG analysis

ECG signal quality was assessed per lead in 10-second segments as good or poor using the method of Kuetche et al. [9]. R-peaks were detected per lead within good-quality segments using a custom Pan-Tompkins–based algorithm. Detections across leads were pooled and merged into a single global R peak per beat, with peaks occuring within 50 ms of one another treated as belonging to the same beat.

2.5. Coronary sinus analysis

For each beat, the atrial component of the CS electrograms was analysed using an atrial activation window −300 to −50ms relative to the R-peak (Figure 1A). The samples within this window were arranged into a 5 × 250 matrix, in which rows correspond to the five CS bipolar electrograms and columns correspond to time samples. Each row was baseline-corrected by subtracting its mean. For pairwise comparisons, two such beat matrices are denoted as A and B.

To identify the predominant SR atrial activation morphology, beats were grouped by morphological similarity using normalised cross-correlation of the vectorised matrices A and B. A common temporal shift τ was applied to all five CS leads of one beat relative to the other, thereby preserving the relative timing between leads. Temporal shifts were restricted to a predefined range of ±20 ms and were applied prior to vectorisation. For each shift, only the overlapping portions of A and B were retained, yielding $A_{\boldsymbol{\tau}}$ and $B_{\boldsymbol{\tau}}$, and the similarity metric was computed as:

$$S(\mathbf{A},\mathbf{B}) = \max_{\tau\in[-\tau_{\max},+\tau_{\max}\ ]} \frac{\mathbf{vec}(\mathbf{A_\tau})\cdot\mathbf{vec}(\mathbf{B}_\tau)}{\|\mathbf{vec}(\mathbf{A_\tau})\|\cdot\|\mathbf{vec}(\mathbf{B}_\tau)\|}$$

where τ denotes the temporal shift, τ_{max} the maximum allowed temporal shift, and $A_{\boldsymbol{\tau}}$ and $B_{\boldsymbol{\tau}}$ the overlapping portions of the two beat matrices after applying the shift.

From the resulting scores, a similarity matrix was constructed for each patient across all beats (Figure 1B). This matrix was then represented as a graph, from which the weakly connected components were identified and the largest connected component retained.

The similarity threshold required for grouping was estimated separately per patient. For a range of candidate thresholds (0.5–0.99), the number of beats included in the largest component was determined, and a knee-point function was used to select the threshold immediately preceding the sharpest drop in beat inclusion (Figure 1C).

Figure 1D shows the atrial activation window of an included and excluded beat, alongside the composite atrial activation window of all the beats in the SR group, represented by the 95th percentile range.

This approach assumed that the majority of beats within the recording were SR beats. The largest morphological group was therefore retained as the SR beat set, and morphologically dissimilar beats were excluded. The resulting dominant morphology was visually inspected to verify that this assumption held. Where a non-SR morphology, such as paced activation, was found to be dominant, the corresponding segment was excluded. The similarity analysis was then repeated on the remaining recording.

The local activation time (LAT) of each CS electrogram was defined as the temporal midpoint between the largest positive and negative deflections of the bipolar electrogram, provided these exceeded a minimum amplitude of 0.15 mV. LAT sequence did not always propagate monotonically along the catheter: in some recordings the earliest deflection occurred at an intermediate electrode pair, with propagation proceeding in both directions from that side. The interelectrode time interval ΔT was therefore defined as the absolute time difference between the LATs of directly neighbouring electrode pairs, yielding up to four values of ΔT per beat (Figure 1E). These were pooled across electrode pairs to account for inter-patient variation in CS anatomy and

catheter depth, and summarised as the median per patient.

2.5. Statistics

Group differences in ΔT were assessed with the Mann–Whitney U test; Spearman's rho was used for correlation with LAVI. Baseline characteristics were compared between AF types using t-tests, Wilcoxon rank-sum tests, or chi-squared tests as appropriate.

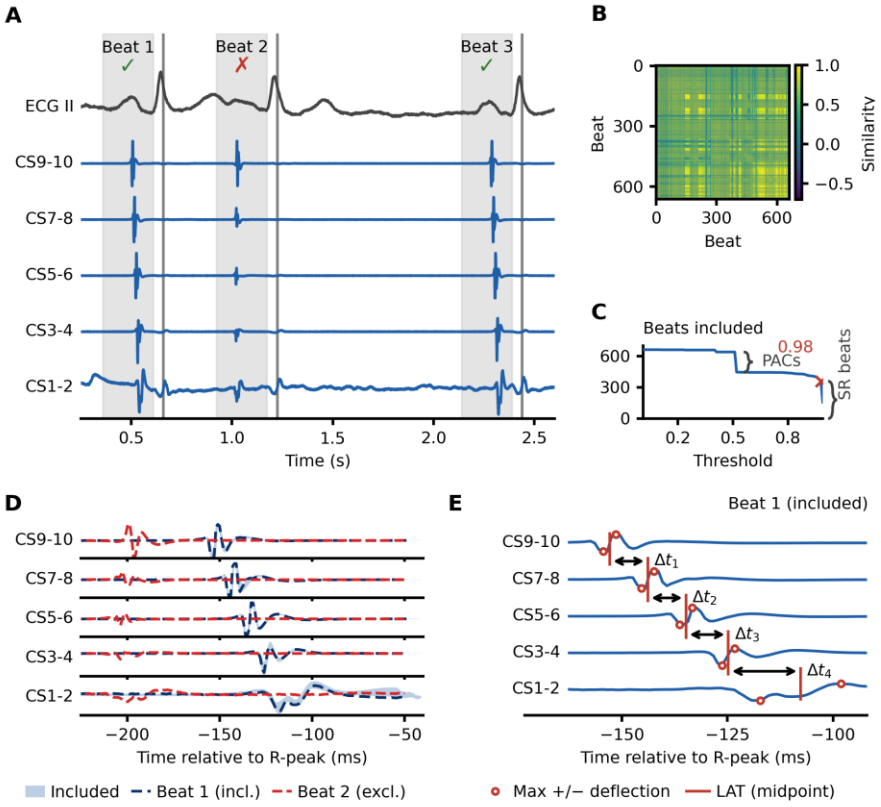

Figure 1 Beat selection and quality assessment for CS signal analysis. ***(A)*** *Example ECG (lead II) together with all five CS bipolar leads (proximal CS9-10 to distal CS1-2), with R-peak annotation (vertical lines) and atrial activation windows (shaded; −300 to −50ms relative to the R-peak). Beats are numbered, with a checkmark or cross indicating inclusion in the sinus rhythm group after beat similarity grouping; beat 2 was excluded.* ***(B)*** *Beat similarity matrix for an example patient, based on the normalised cross-correlation between beats.* ***(C)*** *Threshold selection via knee-point detection; number of beats included in the largest cluster plotted against candidate threshold (0.50–0.99), with the selected threshold marked in red.* ***(D)*** *Shaded region: 95th percentile range of the CS waveform across included beats (N = 359) for a representative patient, per lead. Dashed red: the excluded beat 2 from panel A; dashed blue: the included beat 1 from panel A.* ***(E)*** *Example of local activation time detection and the resulting time intervals, red circles indicate local extrema, red line indicates determined LAT, intervals between the red lines are the interelectrode activation time interval ΔT*

3. Results

3.1. Study population

Of 237 (ISOLATION) and 106 (ISOLATION 2.0) patients meeting the first two criteria (first-time ablation and SR at start of the procedure), 85 and 39 respectively had CS recordings meeting the signal-quality criterion, yielding a combined study population of 124 patients undergoing ablation between August 2020 and December 2025 (ISOLATION: August 2020–August 2023; ISOLATION 2.0: October 2023–December 2025).

3.2. Interelectrode activation time and AF phenotype

The study population comprised 124 patients presenting in sinus rhythm at the start of first-time AF ablation (92 paroxysmal, 32 persistent). ΔT did not differ between AF types: both groups showed a ΔT of 10 ms (IQR 9–11 ms; Mann–Whitney U test, p = 0.538).

LAVI data were available for 102 of the 124 patients. Statistical analysis showed no correlation between CS

interelectrode activation time and LAVI (R = 0.073, p = 0.463) (Figure 2C).

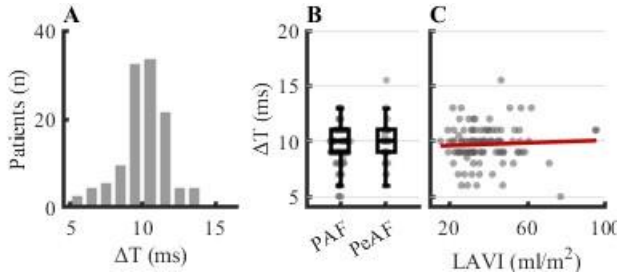

*Figure 2CS interelectrode activation time compared to AF phenotype. **(A)** Distribution of median ΔT for all patients (N = 124); median 10 ms, IQR 9–11 ms. **(B)** Distribution categorised by AF type for paroxysmal (N = 92) and persistent (N = 32) patients. Both groups show a median of 10 ms (IQR 9–11 ms; whiskers 6–13 ms). **(C)** Correlation between CS interelectrode activation time and LAVI (N = 102; R = 0.073, p = 0.463). Each point represents an individual patient. AF, atrial fibrillation; CS, coronary sinus; LAVI, left atrial volume index*

4. Discussion

The intervals were narrowly distributed across patients (IQR 9–11 ms), with limited but non-zero interpatient variation. This variation did not translate into a difference between AF types, with a median of 10 ms in both groups. Given the 10 mm spacing between electrode pairs and the 1 kHz sampling frequency, the temporal resolution may be insufficient to distinguish differences between groups. AF is moreover a progressive disease, for which categorisation into two groups may not capture the continuous process of atrial remodelling. The continuous indicator LAVI, however, also showed no association with ΔT. Left atrial dilatation reflects structural remodelling, which may progress independently of the electrical remodelling of the substrate, underscoring the need for electrophysiological indicators. This is in line with findings in the literature, where atrial conduction intervals predicted recurrence while showing no or only weak associations with atrial dilatation [5,6].

Recordings from only 124 of 343 patients (36%) passed quality screening. Screening was visual, performed by a single observer, and criteria were qualitative and not yet formalised. Blinding to AF type and LAVI makes differential rejection between groups unlikely, but selection toward recordings with favourable catheter position and larger deflections cannot be excluded. Activation sequences suitable for this analysis are not universal. Yamashita et al. observed proximal-to-distal CS activation in 245 of 441 patients [6]. The requirement for an interpretable sequence therefore constrains yield independently of signal quality.

This is a preliminary analysis of an ongoing study. Future work should quantify the variation of ΔT within a patient as well as along the catheter rather than pooling all intervals, formalise the selection criteria, and relate ΔT to other parameters available within the ISOLATION cohorts, including ablation outcome.

These findings do not support ΔT, as defined here, as an indicator of AF type or left atrial dilatation. Whether it reflects other aspects of the atrial substrate remains to be determined.

References

[1] S. Tzeis et al., "2024 EHRA/HRS/APHRS/LAHRS expert consensus statement on catheter and surgical ablation of atrial fibrillation," Heart Rhythm, vol. 21, no. 9, pp. e31–e149, 2024.

[2] M. A. Allessie, J. Ausma, and U. Schotten, "Electrical, contractile and structural remodeling during atrial fibrillation," Cardiovasc. Res., vol. 54, no. 2, pp. 230–246, 2002.

[3] L. Chollet et al., "Impact of atrial fibrillation phenotype and left atrial volume on outcome after pulmonary vein isolation," Europace, vol. 26, no. 4, 2024, Art. no. euae071.

[4] N. Johner, M. Namdar, and D. C. Shah, "Intra- and interatrial conduction abnormalities: hemodynamic and arrhythmic significance," J. Interv. Card. Electrophysiol., vol. 52, no. 3, pp. 293–302, 2018.

[5] Y. Kanemaru et al., "Elongation of the high right atrium to coronary sinus conduction time predicts the recurrence of atrial fibrillation after radiofrequency catheter ablation," Int. J. Cardiol., vol. 300, pp. 147–153, 2020.

[6] D. Yamashita et al., "Time interval from right atrium to coronary sinus predicts postablation atrial fibrillation recurrence in current ablation practice," Circ. J., vol. 89, no. 6, pp. 774–783, 2025.

[7] C. Ozcan et al., "Electrophysiological predictors of susceptible atrial substrate for the onset and recurrence of atrial fibrillation," J. Interv. Card. Electrophysiol., vol. 68, no. 3, pp. 635–642, 2024.

[8] D. V. M. Verhaert et al., "Rationale and design of the ISOLATION study: a multicenter prospective cohort study identifying predictors for successful atrial fibrillation ablation in an integrated clinical care and research pathway," Front. Cardiovasc. Med., vol. 9, 2022, Art. no. 879139.

[9] F. Kuetche, N. Alexendre, N. E. Pascal, and S. Thierry, "Simple, efficient, and generalized ECG signal quality assessment method for telemedicine applications," Inform. Med. Unlocked, vol. 42, 2023, Art. no. 101375.

[10] The MathWorks Inc., MATLAB version R2024b. Natick, MA, USA: The MathWorks Inc., 2024.

Address for correspondence:

Iskander Huijsse
Universiteitssingel 50, 6229 ER Maastricht, The Netherlands
iskander.huijsse@maastrichtuniversity.nl