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Fibrosis Reduces the Coincidence of Repetitive Activation Patterns between the Coronary Sinus and Atrial Regions in Simulated Atrial Fibrillation

Margot van Montfoort[1], Victor Marques[1], Ozan Özgül[1], Ali Gharaviri[2], Simone Pezzuto[3], Angelo Auricchio[3], Pietro Bonizzi[4], Ulrich Schotten[1], Stef Zeemering[1]

[1] Department of Physiology, Maastricht University, Maastricht, The Netherlands
[2]Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom
[3]Center for Computational Medicine in Cardiology, Euler Institute, Università della Svizzera Italiana, Lugano, Switzerland
[4]Department for Advanced Computing Sciences, Maastricht University, Maastricht, The Netherlands

Abstract

Repetitive Atrial Activation Patterns (RAAPs) detected in the coronary sinus (CS) during atrial fibrillation (AF) may represent a reference to construct composite maps of coincident local RAAPs elsewhere in the atria, potentially improving the identification of AF drivers. RAAP coincidence may however depend on AF complexity and may be affected by structural remodeling. Using computer simulations, we investigated coincidence and coupling of RAAPs in the CS and other regions in the atria, in the absence and presence of fibrosis. In our models, the CS displayed highly repetitive behavior unaffected by fibrosis. RAAP coincidence and coupling of other regions in the atria with the CS was high in the absence of fibrosis, but significantly decreased in the presence of fibrosis, most notably in the left atrium. In coincident RAAPs in the CS and atrial regions, quantification of the degree of RAAP coupling is required to provide further confirmation of the validity of employing CS electrograms as a reference for composite RAAPs maps.

1. Introduction

During atrial fibrillation (AF), the atria show complex and variable electrical conduction patterns. Direct contact mapping of these conduction patterns has been of great use to understand mechanisms behind AF and can enable the detection of AF sources. Localization and ablation of these sources may improve outcome in patients with AF. Endocardial mapping of AF can detect repetitive atrial activation patterns (RAAPs) representing potential AF sources, such as focal and re-entry patterns [1]. A spatiotemporally stable AF source may also produce RAAPs in its direct vicinity, or more distal regions of the atria. Recurrence plot (RP) analysis can identify repetitive patterns in a dynamical system [2]. A RP analysis approach identified RAAPs in high-density mapping of AF [3] and was used to quantify their incidence, prevalence, and type of trajectory [4]. However, current electro-anatomical mapping catheters can only cover a small region of the atria at a time, making it challenging to link local RAAPs in sequential point-by-point mapping. Therefore, the coupling between a locally identified AF source and proximal and distal RAAPs cannot be determined reliably.

First attempts have been made to try and connect local RAAPs at sequential recording sites to construct a composite AF conduction map with larger coverage. To combine recordings, evidence is needed that local RAAPs belong to the same larger pattern. A possible technique to address this is the use of continuous recordings from a reference catheter, for instance inserted in the coronary sinus (CS). This concept was tested in a trial by Choudry et al. to create a large scale atrial conduction map [5]. Distinct intervals of repetitive atrial activation were detected in continuous CS electrograms and aligned with intervals in synchronous electrograms of atrial regions. From these aligned regional activation maps, a large-scale conduction vector map was created for each distinct CS activation pattern. The precise methodology underlying this approach was not disclosed, making it difficult to assess the exact degree of association between signals in the CS and sequentially mapped atrial regions.

Due to the physical relation between the CS and the atria, it is hypothesized that RAAPs in the atria are associated with RAAPs of the CS [6]. However, a strong association between RAAPs in the atria and the CS is not guaranteed, may differ per patient and may be affected by fibrotic structural remodelling associated with AF progression. An established association between these RAAPs in the CS and the atria would advocate the use of CS catheter electrograms as a reference for constructing larger maps of AF conduction patterns in the atria.

In this study, we investigate the coincidence and coupling of RAAPs in the CS and other regions in the atria in a three-dimensional anatomical model of AF, in the absence and presence of fibrosis.

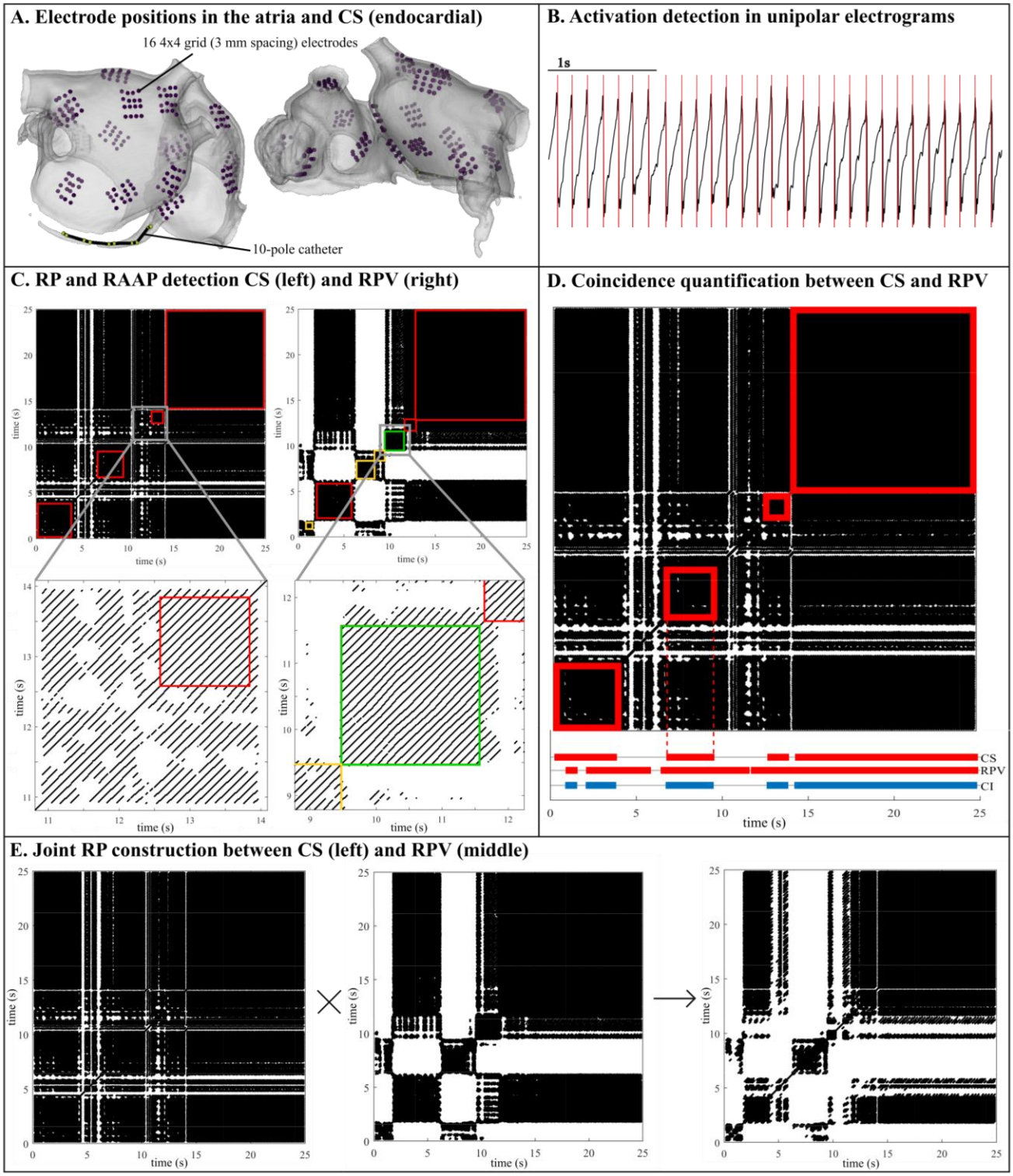

Figure 1. Methodology overview. A) Unipolar electrogram generation from a simulation model with an endocardial 4x4 electrode catheter recording at 16 regions, and a 10-electrode catheter in the CS. B) Activation detection. C) Recurrence plot construction and RAAP detection, colors inidcate unique detected RAAPs.. D) Coincidence quantification between CS and a local regions (RPV), coincidence of 94%. E) Joint recurrence quantification of the CS and RPV, joint RR of 57%. CS: coronary sinus; RP: recurrence plot; RAAP: repetitive atrial activation pattern; RPV: right pulmonary veins; RR: recurrence rate.

2. Methods

Unipolar electrograms were obtained from a detailed, high-resolution three-dimensional model of the human atria which simulates realistic AF electrophysiology and includes atrial wall thickness and intra and inter-atrial structures. Severe fibrosis was introduced by assigning fibrotic tissue conduction properties to 70% of all atrial cells [7]. AF was simulated for 30 seconds in 18 sets of simulations with no (n=7) or severe (n=11) fibrosis. For each simulation, endocardial electrograms were obtained from the CS (10-pole catheter) and 16 locations in the left and right atria (4x4 HD-grid, 3mm spacing) (Figure 1A). To ensure the analysis of stable AF behaviour, the first five seconds after AF induction were removed in all simulated electrograms.

2.1. RAAP detection

This study employed a recurrence analysis pipeline for the analysis of incidence, prevalence, type and trajectories of RAAPs in AF, based on the methodology developed in [3]. Unipolar electrograms obtained from the model were transformed to activation-phase signals by detection of local activations in the electrogram signals (Figure 1B). From these activation-phase signals an activation-phase snapshot can be constructed, resembling an image of the local conduction pattern in a specific location for each time point. All activation-phase snapshots of one recording location were compared with each other in a distance matrix. The distance matrix was transformed to a recurrence plot by applying a maximum distance threshold. To maintain consistency, the maximum threshold was determined for the CS and used for the analysis of the other atrial locations in that simulation. The RPs were eroded to contain only diagonal lines with length of at least one AF cycle (Figure 1C). The percentage of recurrent points, recurrence rate (RR) [2], was calculated for all RPs.

2.2. RAAP coincidence and coupling

Intervals containing RAAPs with a minimum RR of 0.9 per AF cycle were detected by an algorithm that computed the RR per AF cycle in increasing square blocks along the diagonal of the RP [3] (Figure 1C). The detected RAAP intervals in the atrial regions were aligned with those in the CS to identify intervals of coincident RAAPs between each atrial region and the CS. Coincidence (CI) was defined as the percentage of time a coincident RAAP was present in an atrial region during a CS RAAP (Figure 1D). RPs of the CS and atrial regions can be compared to each other by searching for joint recurrences: a simultaneous recurrence in both systems [2] that represent the synchronization, or coupling, of two systems. A joint RP is the eroded product of the non-eroded RPs from the CS and an atrial region (Figure 1E). For each joint RP, we calculated the joint recurrence rate (JRR). The JRR was normalized to the RR of the CS. RR, CI and JRR were compared between the CS, all atrial regions, no and severe fibrosis with a Wilcoxon signed-rank test. A linear mixed-effect model was fitted for both CI and JRR to assess the fixed effects of atrial region and fibrosis as well as their interaction, while taking the random effect of simulation into account.

3. Results

Overall, RAAP prevalence in the CS was high compared to atrial regions (median RR CS: 83% [Q25:73%, Q75:91%], median RR regions: 51% [35%, 63%], $p<0.01$). The presence of fibrosis showed an increased decrease between RAAP prevalence in the CS and atrial regions (median ΔRR no fibrosis: -15% [-4%, -23%], median ΔRR severe fibrosis: -43% [-27%, -53%], $p<0.01$). Similarly, fibrosis reduced CI (median CI no fibrosis: 94% [83%, 99%], median CI severe fibrosis: 72% [46%, 87%], $p<0.01$) as well as JRR (median JRR no fibrosis: 57% [41%, 87%], median JRR severe fibrosis: 31% [16%, 64%], $p<0.01$) of RAAPs in atrial regions with the CS. Especially the left inferior LA and the superior RA regions exhibited a lower RAAP prevalence and coupling with the CS in the presence of fibrosis. The LA septum wall displayed an overall lower RAAP prevalence and coupling with the CS, in both the absence and presence of fibrosis. Figure 2 shows a complete overview of CI and JRR between all atrial regions and the CS.

4. Discussion and conclusion

In this study, we investigated the coincidence and coupling of RAAPs in the CS and different atrial regions during simulated AF episodes in both the absence and presence of fibrosis. In our simulations, the CS displayed highly repetitive behavior. RAAP coincidence and coupling of other regions in the atria with the CS was high in the absence of fibrosis, but significantly decreased in the presence of fibrosis, most notably in the left atrium. Our results provide a proof of principle that coupling between repetitive behavior in the CS and atrial regions is disrupted in the presence of fibrotic structural remodeling. These effects may be more complex in clinical mapping data compared to our simulations, with possible larger variations in RAAP coincidence and coupling between the CS and atrial regions, notably in cases of persistent and chronic AF. Quantification of the exact degree of association between RAAPs in the atria and the CS beyond our approach of RAAP coincidence and joint recurrence rate is required to provide further confirmation of the validity of employing CS electrograms as a reference for composite RAAPs maps.

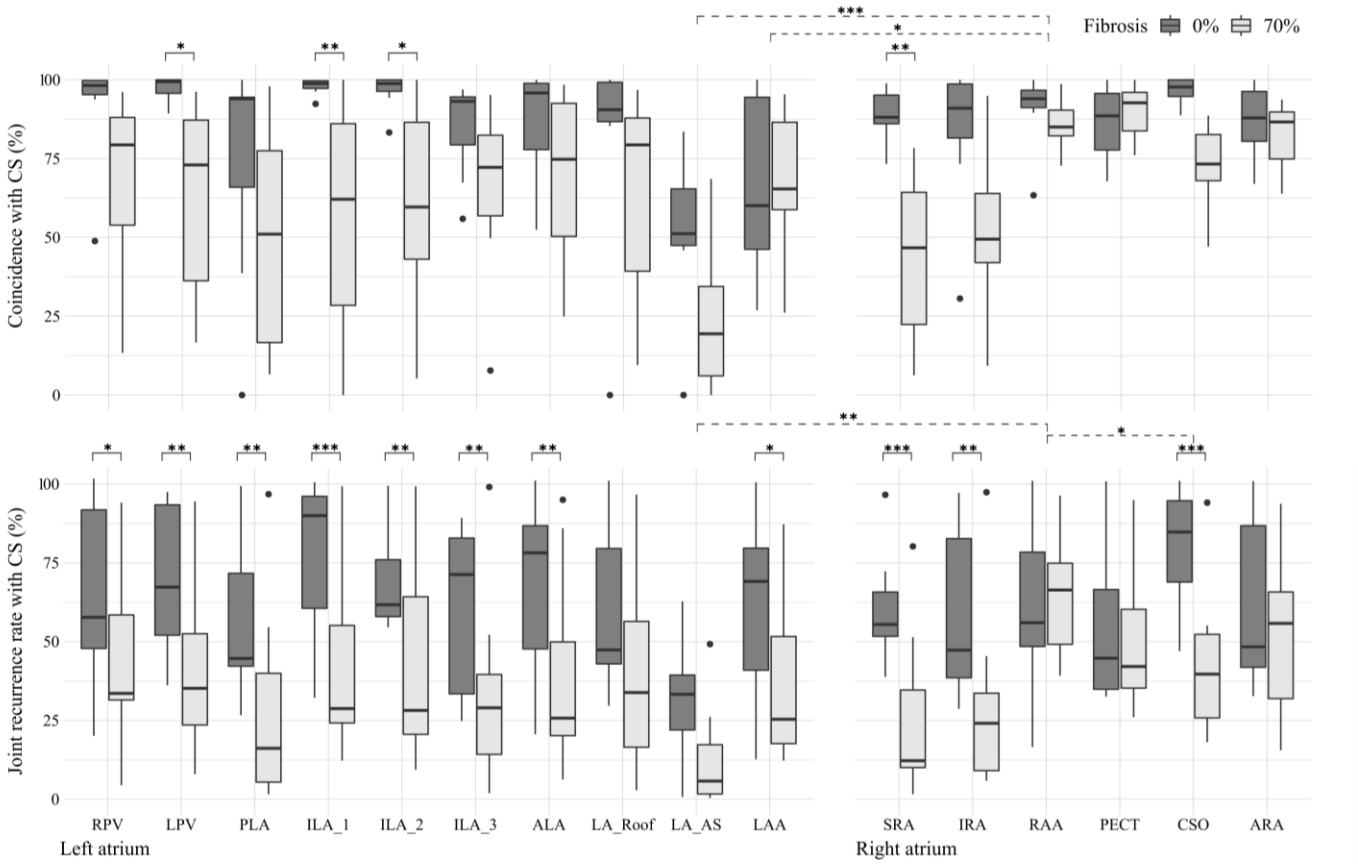

*Figure 1. Coincidence and coupling with CS per atrial region. *** p<0.001, ** p<0.01, * p<0.05. CS: coronary sinus; RPV: right pulmonary vein; LPV: left pulmonary vein; PLA: posterior LA; ILA_1: inferior LA (left); ILA_2: inferior LA (middle); ILA_3: inferior LA (right); ALA: anterior LA; LA_Roof: LA roof; LA_AS: LA septum; LAA: LA appendage; SRA: superior RA; IRA: inferior RA; RAA: RA appendage; PECT: pectinate muscles; CSO: CS ostium; ARA: Anterior RA*

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Address for correspondence:

Stef Zeemering
P.O. Box 616, 6200 MD, Maastricht, The Netherlands
s.zeemering@maastrichtuniversity.nl