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A novel sequential endocardial mapping strategy for locating atrial fibrillation sources based on repetitive conduction patterns: An in-silico study

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ABSTRACT

Background: In persistent atrial fibrillation (AF), localized extra-pulmonary vein sources may contribute to arrhythmia recurrences after pulmonary vein isolation. This in-silico study proposes a high-density sequential mapping strategy to localize such sources.

Method: Catheter repositioning was guided by repetitive conduction patterns, moving against the prevailing conduction direction (upstream) toward the sources. Sources were found either by locally identifying conduction patterns or by encircling the region harboring them. We simulated source tracking in an in-silico atrial model, comparing random vs. upstream-guided catheter repositioning (with and without encircling). To assess performance in increasing AF complexities, we simulated AF in 3 groups: atria with reentry-anchoring scars, without fibrosis, and with severe endomysial fibrosis.

Results: Compared to random mapping, the upstream-guided approach successfully located sources more often (anchored reentries: 70.6% vs. 10.6%; no fibrosis: 87.9% vs. 22.1%; with fibrosis: 95.0% vs. 60.9% of tracking procedures, all $p < 0.001$), using fewer steps (median [IQR]: 11 [7;23] vs. 26 [13;35]; 10 [6;19] vs. 19 [10;27]; 11 [7;19] vs. 16 [8;30], respectively, all $p < 0.05$). Adding source encircling increased source detection (98.1 %, 100 %, and 99.5 %, all $p < 0.01$ vs. local detection only), reducing required steps (9 [6;12], 8 [6;12], and 9 [6;13], all $p < 0.05$). In some cases (11.9 %, 17.1 %, and 10.5 % of procedures), the algorithm encircled regions >15 mm from the source.

Conclusion: Moving mapping catheters upstream improves source detection efficiency, even in the presence of severe fibrosis. Encircling sources may help find regions of interest in fewer steps.

1. Introduction

Ablation of atrial fibrillation (AF) by pulmonary vein isolation (PVI) is an important therapy for rhythm control, achieving high rates of AF freedom in patients with paroxysmal AF [1] and with demonstrated benefits, particularly for early treatment [2]. However, despite advancements in AF ablation over the past years, success rates and long-term outcomes remain suboptimal in patients with persistent AF [1]. The high AF recurrence rates after PVI are not entirely explainable by incomplete ablation scars [3], suggesting that additional mechanisms outside the pulmonary vein area maintain the arrhythmia in a significant proportion of all patients. Several ablation trials targeted potential AF sources outside of the pulmonary veins, such as areas with high dominant frequencies [4], complex fractionated atrial electrograms (CFAE) [5], ectopic foci [6], and functional reentries [6,7]. However, none of these techniques has consistently proven superior to PVI alone [5,8]. Therefore, new and objective approaches for mapping and localizing potential ablation targets are needed.

Localizing potential AF sources is challenging because of the limitations of mapping catheters, including spatial resolution and coverage

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[9], and because of the spatiotemporal instability of sources. While most clinically available high-density mapping catheters possess sufficient spatial resolution to detect stable AF sources [9], the sources that meander in areas larger than the electrode usually remain undetected. Combining sequential maps may identify such sources but is hampered by continuously changing conduction patterns during AF.

However, repetitive and thus more stable conduction patterns have been explored to identify regions frequently harboring AF sources. Repetitive conduction has been demonstrated in potential AF mechanisms such as ectopic foci [10] and reentries [11,12], and could be explored to find such regions of local organization. If these sources are present intermittently or continuously, they are also expected to conduct repetitively to neighboring regions to maintain AF [13]. We hypothesize that this property can be used to guide the repositioning of high-density mapping catheters toward regions harboring sources.

This study introduces a novel mapping strategy to guide high-density catheters toward AF sources based on repetitive conduction patterns. Our approach considers sources as regions within the atria from which continuous or intermittent repetitive conduction patterns propagate to neighboring areas, including various types of sources. To evaluate this approach, we conducted virtual mapping procedures on high-resolution simulations of human AF and studied the efficacy and accuracy of source detection using this algorithm.

2. Methods

The general framework of our proposed mapping strategy is given in Section 2.1, without assuming specific experimental configurations such as catheter type or source detection algorithms. We present the approach for sequentially repositioning a mapping catheter following the dominant conduction direction (Section 2.1.1), and describe requirements for source localization algorithms (Section 2.1.2).

Next, we describe the specifics of our in-silico experimental setting to evaluate that mapping strategy (Section 2.2), including the generation of AF simulations with increasing complexities (Section 2.2.1), how AF sources were localized (Section 2.2.2), the experimental parameters (Section 2.2.3), and how the performance was evaluated (Section 2.2.4).

2.1. General description of the mapping strategy

The proposed high-density sequential mapping procedure is outlined in Fig. 1. Unipolar electrograms (EGMs) are measured sequentially with a high-density mapping catheter. Starting from a given position, the catheter is iteratively moved upstream of the main conduction direction of repetitive activation patterns. This procedure continues until activation patterns corresponding to a source are observed locally or until the mapped positions encircle an area in the atria.

2.1.1. Catheter repositioning

The high-density mapping catheter is moved progressively from the initial position against the prevailing direction of conduction until an AF source is located (see Section 2.1.2). Repositioning is determined by the direction of repetitive conduction at the mapped regions. To detect intervals with repetitive activity, we recently proposed an approach based on recurrence plots, a well-validated method to visualize a profile of the local repetitive behavior in complex non-linear dynamical systems such as AF conduction [13]. Such plots are built from pairwise comparisons between the state of a system over time, with black dots marking two similar time instants given a similarity measure and a threshold. Here, the activation times of an electrode array are compared at different time instants. Blocks of continuous diagonal lines represent patterns repeating during the corresponding time interval (Fig. 2, bottom left).

When repetitive activity is detected, the catheter is moved upstream toward the origin of the last observed repetitive activation pattern. The main conduction direction is determined from the average activation pattern during the last repetitive interval in the recurrence plot (Fig. 2, bottom row). The catheter is moved with a given step size, which depends on the chosen mapping catheter and on the desired level of overlap between adjacent mapped regions. To prevent mapping regions unrelated to the tracked pattern, areas downstream of the conduction pattern are marked to be avoided during mapping. It is possible that no repetitive interval is detected in the recurrence plot. In such cases, the next position is determined randomly, and the previously mapped region is marked to be avoided in future placements (Fig. 2, top row). If there are no more available positions upstream at a given step,

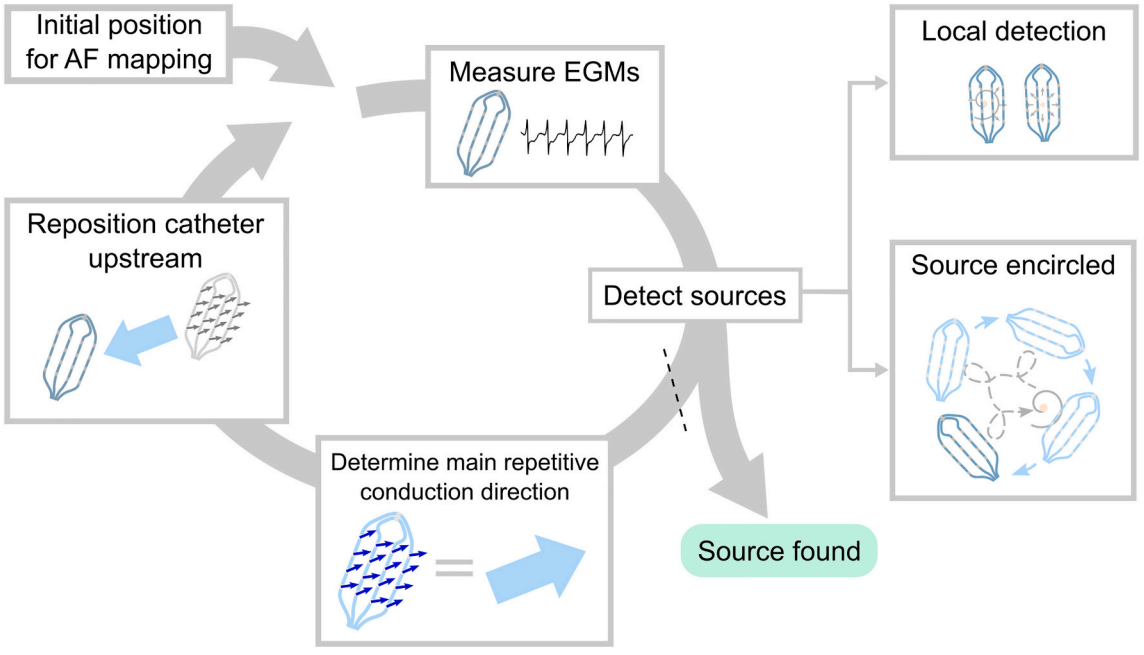

Fig. 1. Overview of the mapping approach. Unipolar atrial EGMs are obtained during AF with a high-density mapping catheter starting from a given initial position. The catheter is moved opposite to the main conduction direction of repetitive activation patterns until a source is detected by either classifying local activation patterns or by encircling the region in which a source is present.

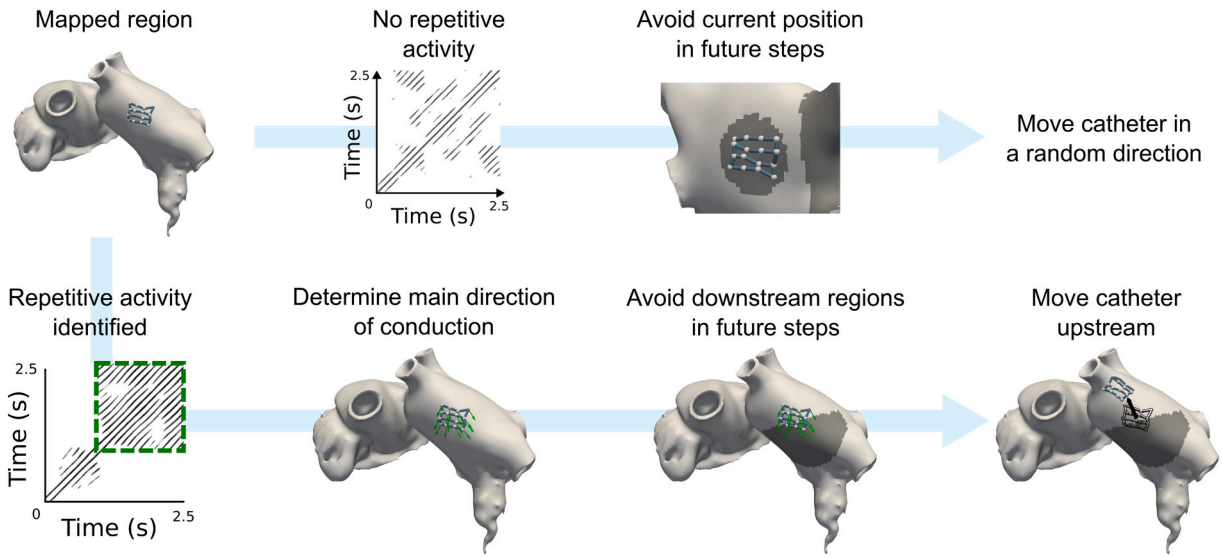

Fig. 2. Strategy for catheter repositioning. If no repetitive conduction pattern is observed in the recurrence plot (top row), only the current position of the catheter is removed from the future available positions to place the catheter (marked in gray). The catheter is then moved in a random direction. Alternatively, if a repetitive activity is identified in the recurrence plot (bottom row), the prevailing conduction direction during the last repetitive interval is determined. The region downstream of the conduction is marked as invalid for future placements, and the catheter is moved upstream of the main conduction direction.

indicating a change in the underlying behavior or tracked source, the avoided regions are reset.

2.1.2. AF source detection

We considered two different strategies for detecting an AF source: local source detection and encircling. The first approach is applicable in the scenario in which the mapping catheter is placed directly on top of a source, which can then be observed within the field of view of the catheter. The proposed mapping strategy does not assume the use of specific source detection algorithms. As such, any or multiple methods to identify AF sources within the field of view of a high-density mapping catheter can be integrated into this pipeline. The choice of algorithm is dependent on the employed catheter and tracked sources in specific cases. Locally detected sources represent a specific mechanism, such as a reentry or focal activation.

The second strategy is designed to detect spatiotemporally less stable AF sources, such as meandering reentries [7], by effectively enclosing the region where these sources are located. This type of source cannot always be observed by the high-density mapping catheters during a single recording interval in a single location. Additionally, repositioning the catheter upstream of repetitive activation patterns may inadvertently lead the catheter around the source instead of directly to its location. This phenomenon can occur with reentrant sources due to the spiral conduction pattern or with focal sources due to the choice of step size, potentially skipping over the actual source.

To ensure the localization of sources in these cases, the encircling criterion uses the information on conduction direction from previously mapped regions to determine the region where a source is likely present. An encircled region was defined as a portion of the atria surrounded by areas that were either previously mapped or marked to be avoided during the catheter repositioning (see Section 2.1.1 and Fig. 2). Sources detected by encircling are not associated with specific conduction patterns, but rather represent a region from which activations repetitively propagated to neighboring areas.

Both the local and the encircling strategies are considered endpoints of a tracking procedure, indicating the position of a source. If a source is detected locally, the center of the mapped region is marked as the source position. Conversely, if a region is encircled, the center of that region is marked as the source position.

2.2. In-silico evaluation of the mapping strategy

2.2.1. AF simulations

To develop and test the proposed mapping strategy, a highly detailed in-silico model of the human atria was used [14]. This bi-atrial volumetric model has a varying wall thickness and includes several intra- and inter-atrial structures, such as the pectinate muscles and crista terminalis, the left atrial appendage bundle network, the Bachmann bundle (BB), and the coronary sinus (CS). Moreover, the model contains realistic fiber orientations, which are different in the endocardial and epicardial layers, and includes electrophysiological characteristics corresponding to the atria of AF patients [14]. This model allows simulating AF driven by sources such as reentries and transmural breakthroughs (BTs) [14].

We generated three groups of AF simulations to capture different levels of complexity observed in AF patients, considering the number and spatiotemporal stability of sources. To control simulation complexity, we modified the atrial substrate with scars or fibrosis (Fig. 3). Additionally, all groups had electrically remodeled action potentials corresponding to a persistent AF patient: using the Courtemanche model to simulate membrane dynamics [15], the conductances for the transient outward current (I_{to}), calcium current (I_{CaL}), and inward rectifier potassium current (I_{K1}) were set at 40, 35, and 200 % of their normal values, respectively [14].

In the first group, to obtain AF with low complexity, we simulated atria with scars that anchored reentries, resulting in simpler conduction patterns. We added a 12-mm radius scar region consisting of non-conductive tissue ingrained with conductive pathways to 8 different regions of the structurally normal atrium (Fig. 3, left). These scars served to stabilize the reentries in different parts of the atrium depending on the simulation. The second group consisted of atria without fibrosis (Fig. 3, middle), leading to more complex AF simulations compared to the first group because no scars stabilized the arrhythmia. The highest degree of AF complexity was achieved in the third group, where fibrosis was introduced to represent patients with severe structural remodeling, associated with more persistent AF cases. Fibrotic properties were assigned to random patches covering 70 % of the atrial surface (Fig. 3, right) [16], where fibrotic elements conducted along fiber orientations, but not across fibers, representing endomysial fibrosis [17].

In the groups without and with fibrosis, AF was initiated by

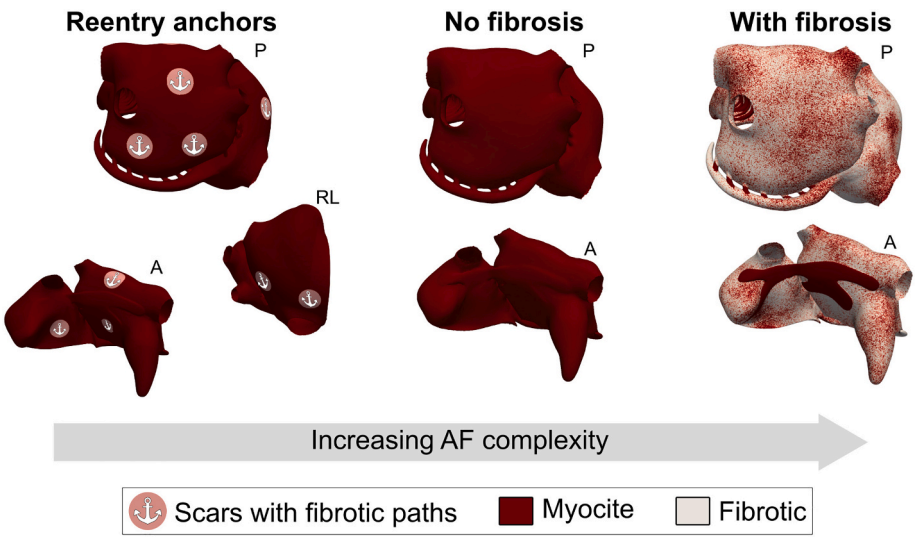

Fig. 3. Substrate modifications of the atria to obtain different levels of AF complexity. The atrial substrate was modified from the baseline without structural remodeling (center) to simulate AF with different complexities. Scars with conductive paths (left), were added to anchor reentries and generate simpler conduction patterns (8 scars in total, 1 per simulation). On the other hand, patches of endomysial fibrosis covering 70 % of the atria (right) were used to represent the progression of structural remodeling with the persistence of AF. A: Anterior view, P: posterior view, RL: right lateral view.

incremental pacing (from 280 to 124 ms) from 20 selected locations. When initiated, AF was simulated for 30 s, and EGMs were measured in 2.5-second intervals. Shorter 11-second simulations were generated for the group with anchored reentries since the patterns were more stable. In this group, AF was initiated with a temporary block line leading to the scar regions, which was removed after 200 ms, generating a reentry. EGMs were measured in 1-second intervals in this group.

For all the simulations, the transmembrane potentials and extracellular currents were calculated with a spatial resolution of 0.2 mm and a sampling frequency of 1 kHz. Endocardial unipolar EGMs along the whole atrial surface were obtained by calculating the forward solution with 1 mm resolution and sampled at the electrode grid resolution during the mapping. If the mapping required more steps than available segments in the simulations, the data were sampled again from the beginning of the simulation.

2.2.2. *AF source localization*

The locations of simulated reentries and BTs were obtained from the transmembrane potentials to ensure maximal spatial resolution. The rotational cores of functional reentries were localized by tracking phase singularities on the transmembrane potentials at each time step [18]. Phase singularities were clustered spatially (within a 4 mm radius) and temporally (within a 10 ms window) and tracked over time. Only phase singularities lasting longer than 3 AF cycles (AFCL) were considered in this study. The spatial stability of reentries (i.e., degree of meandering) was measured as the area a phase singularity occupied during its lifespan (in mm^2).

A BT was defined as a small wave appearing in the endocardial layer that could not be explained by the propagation of other waves in the same layer. A wave was defined as a group of connected elements with a transmembrane voltage higher than −60 mV. A wavefront was defined as the portion of the wave with a voltage higher than −20 mV. Small waves in the endocardium that corresponded to wavefronts in the epicardium were marked as BT candidates. If this wave increased in size within a period of 10 ms without merging with a larger wave, it was considered as a true BT [14].

The source locations were used as a gold standard to assess whether a source could be correctly detected during mapping procedures.

2.2.3. *Virtual mapping procedures*

We conducted virtual mapping procedures employing a virtual catheter composed of a 4 × 4 electrode grid with 3 mm spacing, resembling the HD-Grid catheter (Advisor HD-Grid Mapping Catheter, Sensor Enabled, Abbott, St. Paul, MN), which was used to record unipolar EGMs from the simulations. The mapping procedures were restricted to a single atrium, based on the choice of initial position. Because of this constraint, if no source was present in the mapped atrium, a radial spread of activations should be detected in one or more of the regions connecting both atria (BB, septum, CS, or posterior connections).

Activation times were detected on the simulated EGMs based on a maximum negative deflection approach and used to calculate the AFCL, conduction direction and velocity, and to generate the recurrence plots. Conduction patterns that appeared for at least 3 consecutive AF cycles were considered repetitive. By averaging the conduction velocity direction vectors over all electrodes during the time course of a repetitive activity, the main conduction direction was determined. Catheter repositioning was performed as described above, with fixed 10 mm steps when repetitive activity was detected. This step size ensured that mapped regions were closely adjacent to each other. If no repetitive activity was detected, the step size was reduced to 5 mm. To assess the importance of the step size choice, we also evaluated the performance with a fixed 5 mm step.

Instead of employing a specific algorithm to detect sources during these virtual procedures, we utilized the source locations as determined above to establish a benchmark for the performance of any source detection algorithm. We considered a source as locally detected if was within the field of view of the electrode grid for longer than 3 AFCLs during the recording interval. In this way, we can determine sources that would likely be detected by any technique without constraining the evaluation of the tracking approach to the performance of specific algorithms.

Virtual mapping procedures were conducted under different conditions to evaluate the individual impacts of the catheter repositioning and source encircling strategies. First, we compared mapping procedures repositioning the catheter upstream of the main conduction direction (i.e., upstream-guided) to procedures where the catheter was randomly repositioned in 10 mm steps, avoiding previously visited areas. Twenty mapping procedures were conducted per initiated AF simulation in all complexity levels, for both repositioning strategies. Each mapping procedure started from different positions uniformly spaced along both atria (Supplementary Fig. S1) and was limited to 50 steps, after which

the detection was defined as a failure. Afterwards, we compared the performance of upstream-guided procedures including or not the encircling approach to detect sources, in the same simulations. Also, here, 20 mapping procedures were conducted per AF simulation in all complexity degrees, with the same initial conditions as above.

2.2.4. Performance evaluation

The performance of the mapping strategy was evaluated based on the percentage of tracking procedures leading to sources, the number of steps required to locate a source, and the distance between the mapped source positions and their true locations. To assess the detection accuracy, the mean distance between a reentry or BT at the time of detection and the center of the indicated position was calculated.

Statistical comparisons between pairs of simulation groups or detection methods were performed using Mann-Whitney *U* tests. Categorical comparisons were made with the chi-square test. The significance level for all tests was set at 0.05. Results were expressed as median and [interquartile range].

3. Results

3.1. AF inducibility and source characteristics

AF was initiated in all simulations in the scar anchor group ($n = 8$) using temporary block lines. The generated reentries were anchored to the scar regions in all simulations. In two cases, other reentries appeared elsewhere in the atria and dominated the conduction, with a reentry intermittently being present at the scar region. The reentries in this group meandered in a median area of 87.5 [66.2; 183.2] mm^2 with an AFCL of 139.3 ± 0.8 ms.

In the group without fibrosis, AF was initiated in 35 % of the cases ($n = 7$ out of 20 simulations), with an AFCL of 137.0 ± 0.7 ms ($p < 0.01$ vs. the scar anchor group). During sustained AF, a median of 2 [1; 3] coexisting reentries lasting >3 AFCLs were present, meandering in an area of 127.5 [82.0; 216.0] mm^2 ($p = 0.18$ vs. the scar anchor group). In the group with fibrosis, the AF initiation rate was 55 % ($n = 11$ out of 20 simulations), with a significantly higher number of coexisting reentries (3 [2; 5], $p < 0.001$) compared to the group without fibrosis. The AFCL was 139.3 ± 0.9 ms in this group ($p = 0.88$ vs. the scar anchor group, $p < 0.01$ vs. the group without structural remodeling). These reentries meandered in an area of 188.0 [121.2; 305.5] mm^2 ($p < 0.05$ compared to both other groups).

3.2. Guiding the catheter upstream of the main conduction directions was crucial to detect sources efficiently

With the 20 starting positions per simulation and 8 initiated AF simulations, 160 mapping procedures were conducted in the group with anchored reentries by randomly repositioning the catheter, and another 160 procedures were conducted by following the repetitive conduction patterns upstream. Similarly, 140 and 220 tracking procedures were performed for the groups without and with fibrosis, respectively, in each of the random and conduction direction-guided mapping approaches.

Examples of successful detections with the random and upstream-guided mapping procedures are shown in Fig. 4. In contrast to the random mapping approach (Fig. 4A), informing the repositioning by the conduction direction led the catheter to the region where a reentry was present in fewer steps (Fig. 4B). In some cases, moving the catheter upstream of the conduction direction required a relatively high number of steps to locate the source (Fig. 4C). This effect is associated with the limited field of view of the catheter and the step size. With a fixed step and limited field of view, positioning the grid exactly on top of the

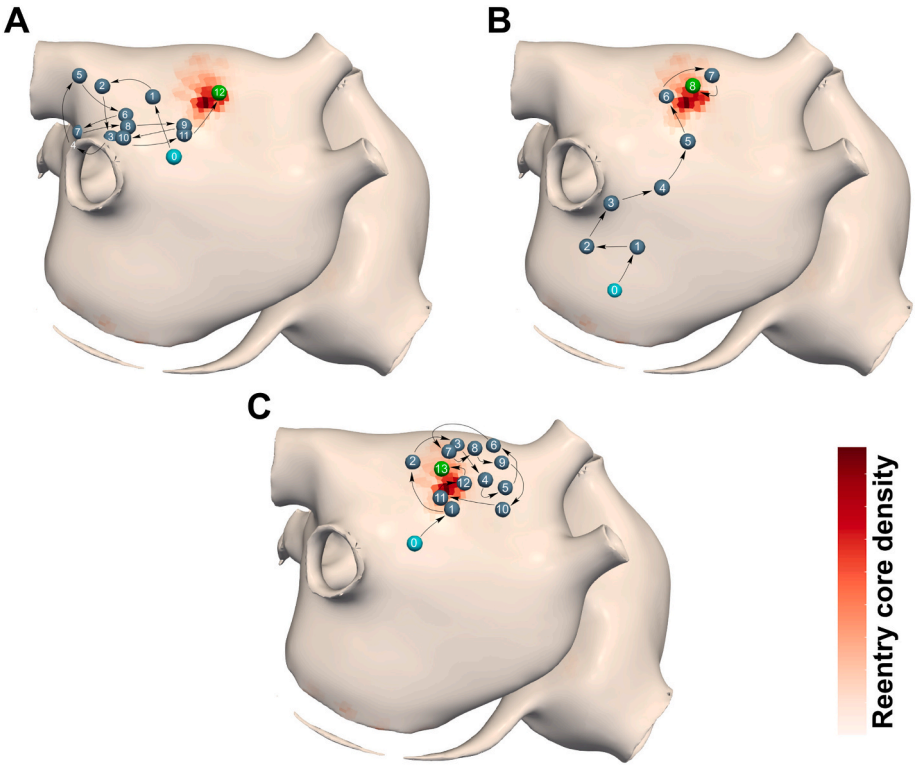

Fig. 4. Examples of mapping procedures with the random (A) and upstream-guided (B, C) mapping approaches on the same simulation with an anchored reentry. Informing the repositioning of the catheter by the conduction patterns quickly led to the reentry anchored to the posterior wall (B, C), which does not happen with random mapping even if the source is eventually located. However, due to limitations in the field of view and the fixed step size, many steps may be required until the catheter is exactly on the source (C). The circles mark the center of the electrode arrays at the numbered time step; a cyan circle represents the starting position, while a green circle symbolizes the place where a source was localized. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

source may require several steps.

The efficiency of guiding the catheters upstream of repetitive conduction patterns is reflected in the number of detected sources and required steps to find a source (Fig. 5). Considering the limitation of 50 steps, the conduction direction-guided procedure detected a significantly higher number of sources in all groups compared to the random approach (Fig. 5A): moving upstream resulted in 113 vs. 17 procedures with detected sources (70.6 % vs. 10.6 %, $p < 0.001$) in the group with anchored reentries, in 123 vs. 53 sources (87.9 % vs. 22.1 %, $p < 0.001$) in the group without fibrosis, and in 209 vs. 134 sources (95.0 % vs. 60.9 %, $p < 0.001$) in the group with fibrosis. Additionally, moving the mapping catheter upstream also required fewer steps to find a source in all groups (Fig. 5B). A source was located using 11 [7; 23] vs. 26 [13; 35] steps ($p < 0.05$), 10 [6; 19] vs. 19 [10; 27] steps ($p < 0.001$), and 11 [7; 19] vs. 16 [8; 30] ($p < 0.01$) steps for the groups with anchored reentries, without fibrosis, and with fibrosis, respectively. Similar improvements in mapping efficiency are observed with the finer step size of 5 mm (Supplementary Fig. S2).

3.3. *Encircling sources further increased the number of detected sources while requiring fewer steps*

The effect of including source encircling as a criterion for their detection, in addition to guiding the catheter upstream, is illustrated in Fig. 6A. Procedures starting from the same position in a simulation of the group without fibrosis are shown without (left) and with (right) encircling. Including encircling allowed the procedure to stop when a region harboring a source was encircled. Figs. 6B and C show further examples of encircling in simulations without and with fibrosis, respectively. In these examples, regions with reentries were localized even with their increasing meandering areas and instability, also in the RA.

When including the encircling criterion, 69.4 % of sources were detected by this method in the group with anchored reentries. In the groups without and with fibrosis, 45.0 %, and 43.4 % of the sources were detected by encircling, respectively. Tracking procedures including the encircling approach led to the localization of more sources within the 50-step limit compared to the method applying only local detection (Fig. 7A): in the group with anchored reentries, 157 vs. 113 (98.1 % vs. 70.6 %, $p < 0.001$) sources were localized, respectively. For the groups without and with fibrosis, these approaches led to 140 vs. 123 (100.0 % vs. 87.9 %, $p < 0.001$) and 219 vs. 209 (99.5 % vs. 95.0 %, $p < 0.01$) localized sources, respectively. Including the encircling criterion reduced the required number of steps, leading to faster source detections compared with the group with only local detection: 9 [6; 12] vs. 11 [7; 23] ($p < 0.001$), 8 [6; 12] vs. 10 [6; 19] ($p < 0.05$), and 9 [6; 13] vs. 11 [7; 19] ($p < 0.001$) steps were required to find a source in the groups with reentry anchoring, without, and with fibrosis, respectively. A detailed description of the closest sources at the time of detection is displayed in Supplementary Fig. S3, with the mapping approach performing similarly for reentries and breakthroughs.

Despite the improvements in the number of localized sources and steps, some of the encircled regions were distant from reentries or breakthroughs at the time of their detection (Fig. 8A), since encircling does not take into account the specific mechanisms in the encircled area.

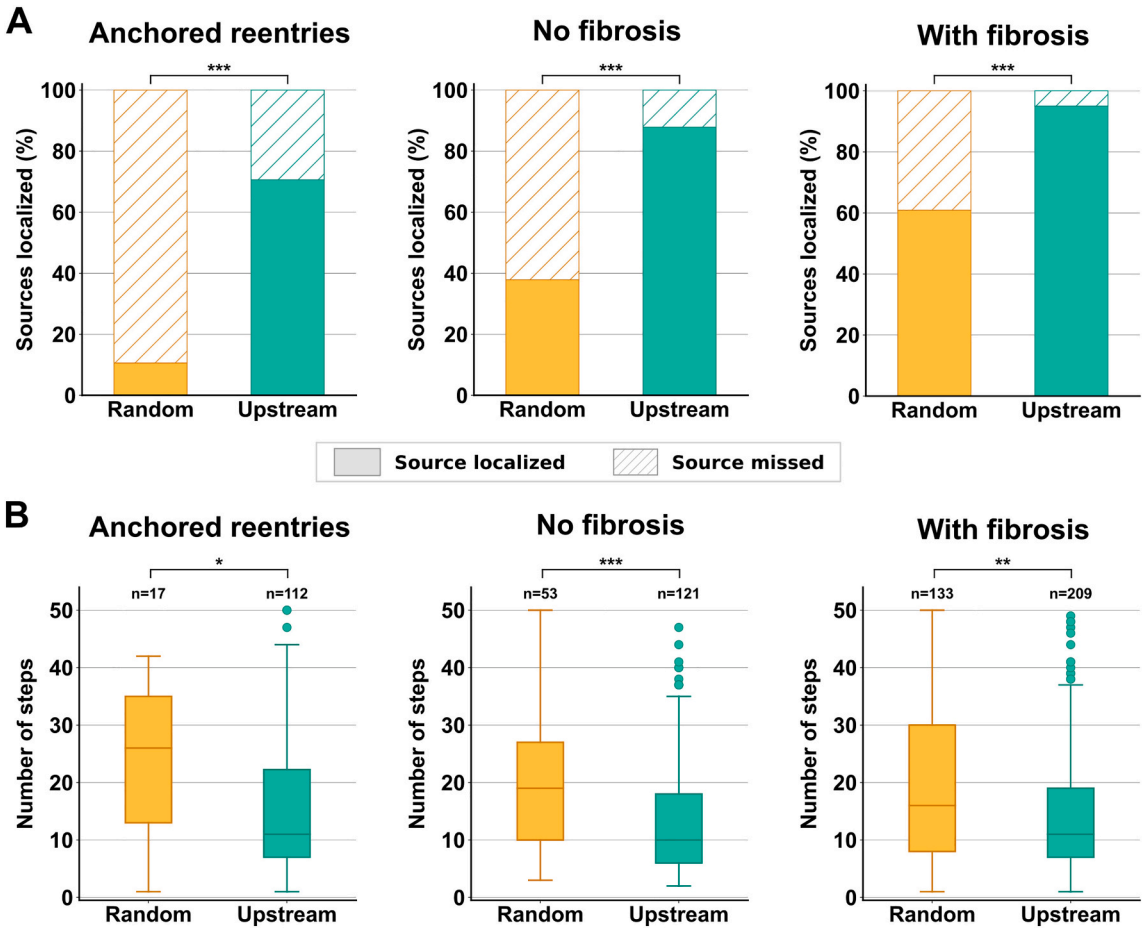

Fig. 5. Comparison between tracking procedures with random and upstream-guided catheter repositioning Guiding the catheter upstream of the conduction direction significantly improved the number of localized sources (A), which were detected in significantly fewer steps (B), in all simulation groups. Boxes represent the inter-quartile range (IQR); whiskers extend from the box to the farthest data point lying within 1.5xIQR from the box. Chi-square (A) and Mann-Whitney U (B) tests, significant differences: $\star = p < 0.5$, $\star\star = p < 0.01$, $\star\star\star = p < 0.001$.

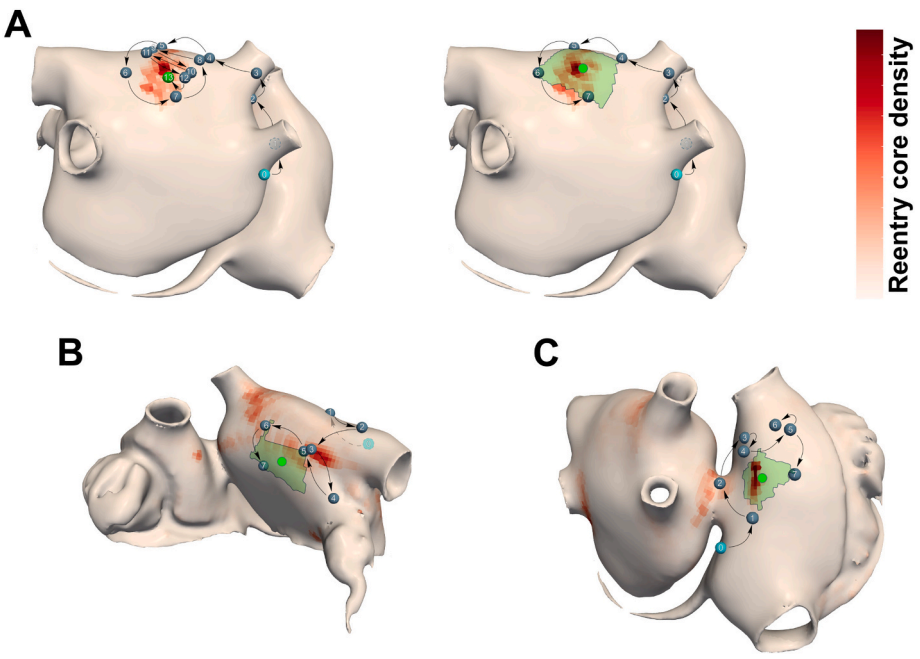

Fig. 6. Examples of mapping procedures. Including the encircling criterion allowed source detection even if the catheter was not placed directly at the source location (A, left without encircling vs. right with encircling for the same simulation and initial position). Encircling led to the detection of regions where sources were frequently present in simulations without (B) and with (C) fibrosis, including in the right atrium.

For the group with anchored reentries, 19 procedures (11.9 %) led to encircled areas further than 15 mm from one of these mechanisms. In the groups without and with fibrosis, 24 (17.1 %) and 23 (10.5 %) of the procedures encircled regions >15mm from a reentry or breakthrough, respectively. This happened due to the dynamic behavior of AF, as is exemplified in Fig. 8B. This figure depicts a reentry that was anchored below the left inferior PV but meandered around the vein at the indicated times. The highlighted regions were affected by this dynamic change as the direction of the repetitive conduction patterns changed. Regions 1 and 2 identified areas where the source was transiently present, while Region 3 identified the original anchoring site when the reentry was no longer there. Fig. 8B summarizes the reasons behind the encircled regions farther than 15 mm from sources at the time of detection, for each simulation group. Most such detections were associated with instability of reentries. Some of the regions were on the septal wall of the atria, where frequent transient reentries appear and from which activations may propagate from the contra-lateral atrium (Supplemental Video 1).

Increasing the sequential mapping density by reducing the step size to 5 mm favored the local detection of sources, with encircling becoming less likely in all groups (Supplementary Fig. S4). Because of this, there were no significant differences between the groups with only local detection versus local detection with encircling.

4. Discussion

We designed a novel mapping strategy to locate areas in the atria potentially driving AF by using information on repetitive conduction directions from sequential high-density maps. We used an in-silico environment to test and validate the proposed strategy by exploiting the knowledge about the underlying conduction patterns. Results show that repositioning the mapping catheter by following upstream the prevailing conduction direction can quickly lead to an AF source, which can be detected directly or by encircling with sequential positioning of the recording catheter. Our findings also show that focusing on repetitive activation patterns from sequential recording sites is fundamental for identifying areas where sources are present, thereby potentially overcoming the important limitation of the field of views of clinically available high-density mapping catheters.

In recent years, numerous studies have observed organized mechanisms that may be considered sources of initiation and maintenance of AF. These mechanisms include ectopic foci [10], stationary [6,19] or meandering functional reentries [7], and transmural breakthroughs [11]. Here, we defined a source as a region from which activations propagate to neighboring areas without assuming a specific underlying mechanism. A similar definition was used in the recently proposed STAR mapping study, where sites of earliest activations were targeted during ablation, with promising initial results for AF termination [20]. We included the criterion of the repetitiveness of the conduction patterns, thus focusing on AF sources characterized by a certain degree of spatiotemporal stability. By adopting this criterion, we specifically tracked sources that showed sufficient stability to be potential ablation targets, thus distinguishing them from highly meandering or transient sources.

Mapping the atria without considering the conduction patterns is unlikely to lead to a source maintaining AF, as demonstrated by our results with reentries and transmural breakthroughs. Even though the likelihood of finding a source randomly increases with the complexity of AF, guiding the repositioning of the catheters upstream of the conduction patterns largely increased the efficacy of source localization. Prior in-silico investigations have similarly implemented upstream-guided methodologies for source localization, demonstrating their efficacy [21,22]. The present study builds upon the previous research by including a wider range of AF complexity in the simulations. Moreover, we propose a catheter-independent algorithm that can incorporate multiple source detection algorithms and address issues of AF dynamics by focusing on repetitive activity. Finally, we explored source encircling as an additional detection strategy to help overcome the limited spatial coverage and demonstrated that this method can significantly contribute to source detection.

To this end, our results demonstrate that encircling sources with subsequential mapping positions may lead to a higher number of localized sources in a lower number of steps. However, encircling also identified regions that were not harboring sources at the moment of

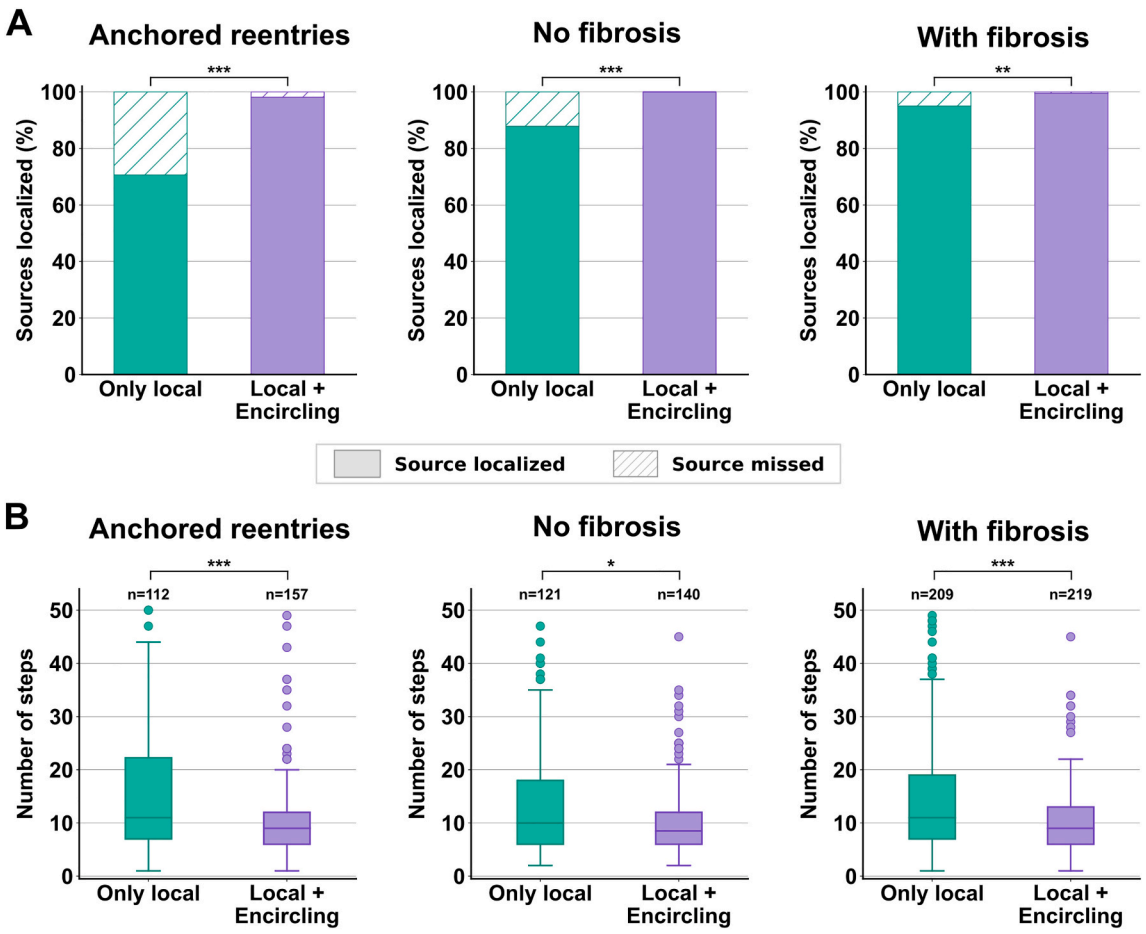

Fig. 7. Performance comparison of upstream-guided catheter repositioning strategies without and with the encircling criterion to detect sources Using the encircling approach led to even more detected sources when compared with the mapping procedures that only allowed local source detection (A). The sources were also found in significantly fewer steps (B), in all simulation groups. Boxes represent the inter-quartile range (IQR); whiskers extend from the box to the farthest data point lying within 1.5xIQR from the box. Chi-square (A) and Mann-Whitney U (B) tests, significant differences: $\star = p < 0.5$, $\star\star = p < 0.01$, $\star\star\star = p < 0.001$.

detection in a few mapping procedures. This happens because the encircling algorithm does not attempt to identify specific conduction patterns, but rather a region from which activations consistently propagate. Such regions may be relevant to AF maintenance, for instance, by repetitively harboring transient reentries. Evaluating the effect of ablating these areas may reveal crucial insights for personalized treatments but was not in the scope of the current study. Complementary tools enabling the identification of the specific sources within the encircled areas, such as high-density and high-coverage composite maps [23], may help clinicians interpret the relevance of these regions for ablation.

The proposed mapping algorithm is robust against increasing conduction complexity resulting from AF-related changes in the atrial substrate, such as the presence of fibrosis [17]. However, it is likely that not all persistent AF patients would benefit from this approach due to the underlying assumption of localized sources that could be targeted by ablation. Patients in which AF is maintained by anarchical mechanisms such as multiple wavelets or by highly meandering reentries would not benefit from this strategy to find localized sources. Nevertheless, the results suggest that our method remains applicable for the subgroup of patients that have stable mechanisms maintaining the arrhythmia, even in the presence of a high degree of atrial fibrosis. The mapping approach utilized in this study relies on essential information readily accessible in current commercial mapping systems, including EGMs, activation times, and conduction direction (e.g., Deno et al. [24]). Importantly, it is not limited to unipolar EGMs. This compatibility greatly facilitates the practical implementation of our proposed approach in clinical settings, empowering electrophysiologists to effectively identify functional mechanisms underlying AF.

4.1. *Limitations*

While the signal processing techniques proposed here are readily available in clinical practice, our results are based on an in-silico model of AF, which, while providing a suitable set-up for validation, may not represent the full extent of the complexity encountered in human AF. Moreover, reentries and transmural BTs are not the only possible mechanisms of AF maintenance. Our method accurately identifies functional mechanisms of AF, but it does not determine the role of these sources in the maintenance of the arrhythmia. To determine their impact, future studies are necessary to assess the relevance of each individual source, either by ranking their importance in generating and maintaining AF or by evaluating whether their ablation terminates and/or prevents the initiation of AF. In the present study, we did not investigate the efficiency of ablating encircled regions or the best strategies for ablating the localized sources. We also did not evaluate specific algorithms for local source detection, which may impact the overall performance of this approach.

5. Conclusion

Repositioning mapping catheters upstream of the leading conduction direction and combining sequential recordings may increase the efficiency and accuracy of mapping procedures for the identification of AF

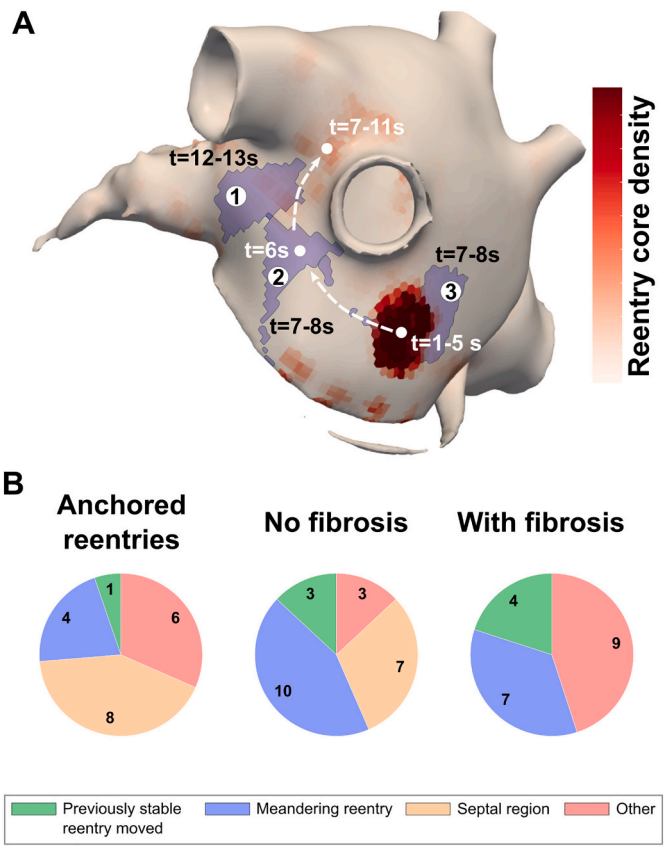

Fig. 8. Examples of encircled regions far from sources at the time of detection. In the example in A, a previously stable reentry meandered around the pulmonary veins (indicated by the trajectory and times in white). The regions encircled during the mapping procedure (in purple) were detected in timesteps in which the reentry was no longer present at the mapped area. In Regions 1 and 2, the reentry was only transiently present, while in Region 3 the reentry was anchored but meandered away. In B, the reasons for encircled regions distant from sources at the time of detection are discriminated per simulation group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

sources. Encircling sources may help to overcome the limitations in spatial coverage of the currently available mapping catheters by reducing the number of mapped regions, even though this may lead to reduced accuracy in source localization in a few cases. The proposed mapping approach is robust against the increase in AF complexity associated with substrate remodeling. Future studies should be conducted to assess the effect of ablation of the localized regions.

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CRediT authorship contribution statement

Victor Gonçalves Marques: Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing, Formal analysis. **Ali Gharaviri:** Methodology, Software, Writing – review & editing, Investigation. **Ozan Özgül:** Writing – review & editing. **Simone Pezzuto:** Conceptualization, Funding acquisition, Resources, Writing – review & editing. **Angelo Auricchio:** Resources, Writing – review & editing. **Pietro Bonizzi:** Supervision, Writing – review & editing. **Stef Zeemering:** Project administration, Supervision, Writing – review & editing. **Ulrich Schotten:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

- **Victor G. Marques:** None declared
- **Ali Gharaviri:** None declared
- **Ozan Özgül:** None declared
- **Simone Pezzuto:** None declared
- **Angelo Auricchio:** None declared
- **Pietro Bonizzi:** None declared
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- **Ulrich Schotten:** US received consultancy fees or honoraria from Università della Svizzera Italiana (USI, Switzerland), Roche Diagnostics (Switzerland), and research grants from Roche and EP Solutions Inc. (Switzerland). US is co-founder and shareholder of YourRhythmics BV, a spin-off company of the University Maastricht.

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