Estimating refractory periods during atrial fibrillation based on electrogram cycle lengths in a heterogeneous simulation setup

Abstract: Acquiring adequate mapping data in patients with atrial fibrillation is still one of the main obstacles in the treatment of this atrial arrhythmia. Due to the lack of catheters with both a panoramic field of view and sufficient electrode density for simultaneous mapping, electrophysiologists are forced to fall back on sequential mapping techniques. But, because activation patterns change rapidly during atrial fibrillation, they cannot be mapped sequentially. We propose that mapping tissue properties which are time independent, in contrast, allows a sequential approach. Here, we use the shortest measured electrogram cycle length to estimate the effective refractory period of the underlying tissue in a simulation study. Atrial fibrillation was simulated in a spherical model of the left atrium comprised of regions with varied refractory period. We found that the minimal measured electrogram cycle length correlates with the effective refractory period of the underlying tissue if the regions with distinct refractory properties are large enough and if the absolute difference in effective refractory periods is sufficient. This approach is capable of identifying regions of lowered effective refractory period without the need for cardioversion. Those regions are likely to harbor drivers of atrial fibrillation, which emphasizes the necessity of their localization.

Keywords: cardiac modeling, atrial fibrillation, substrate mapping, effective refractory period, heterogeneity.

1 Introduction

Current mapping strategies for ongoing atrial fibrillation (AFib) suffer from the inadequacy of existing clinical equipment for simultaneous activation mapping. The spatial resolution of panoramic mapping catheters is not sufficient for the spectrum of wavelengths that occur during AFib. High resolution catheters, in contrast, are sufficient to map the spatial complexity of fibrillation, but offer a limited field of view and thus fail to capture the entire atrium. Sequential local activation time (LAT) mapping solves this problem for periodic rhythms by aligning the signals based on a common reference. However, sequential acquisition cannot be employed for the rapidly changing patterns during AFib. In contrast to activation mapping, substrate mapping avoids this drawback by analyzing constant tissue properties. Existing methods for substrate mapping such as voltage mapping, dominant frequency mapping or CFAE mapping do not directly reflect a tissue property. Here, we investigate the potential and limitations of the distribution of measured electrogram cycle lengths (CLs) to derive information about the effective refractory period (ERP) of the underlying tissue during sequences of ongoing AFib. We hypothesize that the spatial variability of ERP characteristics is of high clinical interest as studies have shown its relevance to the maintenance of AFib [1].

2 Methods

2.1 Spherical model of the left atrium

A spherical geometry was chosen to represent the left atrium as shown in Figure 1 a. Projecting 76 ml as a lower estimate of the left atrial volume in patients with and without AFib [2] to a sphere resulted in an endocardial diameter of 52 mm.

According to a magnetic resonance study [3], the wall thickness was modeled with 1 mm. A 10 mm tissue bath lined the endocardial surface. The average side length of an element in the tetrahedral mesh at the endocardial and epicardial surface was 0.6 mm and increased to 0.8 mm towards the inner boundary of the bath.
The diameters of the left superior pulmonary vein, left inferior pulmonary vein, right superior pulmonary vein (RSPV), and right inferior pulmonary vein (RIPV) were set to 10.0 mm, 9.4 mm, 11.9 mm, and 12.7 mm respectively [4]. The mitral valve (MV) opening measured 32.5 mm in diameter.

The imposition of transmural, circular shaped regions with different tissue properties at the posterior wall of the left atrium completed the geometric setup. The regions comprised all cells within a sphere of specified radius centered at a surface point of the model. The radii ranged from 9 mm to 19 mm in steps of 2 mm width. The circular region was termed area 2, whereas the remaining substrate was referred to as area 1 (see Figure 1 a).

### 2.2 Cell membrane models

The Courtemanche-Ramirez-Nattel (CRN) model of human atrial myocytes [5] served as a basic model and was modified in order to induce AFib-related remodeling. $I_{Na}$ was reduced by 65%, $I_{Kr}$ and $I_{Kr}$ were increased by 100%, $I_{Kur}$ was reduced by 50%, $I_{Ca,L}$ was reduced by 55%, $I_{Na, Ca}$ was increased by 60%, the SR leak current was increased by 50% and the cell capacitance was increased by 20% as described previously for patients suffering from chronic AFib [6]. This level of remodeling will be referred to as level 3 in the following.

Additionally, two weaker and two stronger levels of remodeling were introduced. Knowing that the ERP strongly depends on $I_{Ca,L}$ and $I_{K1}$, these currents were altered. This choice was motivated by the desire to obtain macroscopic differences in ERP rather than to represent different degrees of remodeling biophysically accurately. Table 1 summarizes the five levels of remodeling and the respective changes in $I_{Ca,L}$ and $I_{K1}$ relative to the standard CRN model. $I_{Na}$, $I_{Kr}$, $I_{Kur}$, $I_{Na, Ca}$, the SR leak current and the cell capacitance were kept as described for level 3. To ensure that differences observed in the activation patterns are solely due to differences in ERP and not conduction velocity (CV), the intracellular conductivity was tuned for each cell membrane model to obtain the same CV for single planar excitation waves.

ERPs were investigated in a 1D tissue strand. After initializing the model in a single cell and subsequently in a monodomain environment for each basic cycle length (BCL), stimuli with increasing time delay were applied starting from a short interval. The shortest stimulus time delay evoking a propagating action potential was considered the ERP corresponding to the current BCL [6].

### 2.3 Bidomain simulations

Excitation propagation as described by the cardiac bidomain equation was computed using the software acCELLerate [7] with a fixed time step of $10^{-5}$ s. The output time resolution was $10^{-3}$ s. Transmembrane voltages (TMVs) as well as extracellular potentials (EGMs) were calculated. Exemplary signals are shown in Figure 2. An exemplary TMV map is depicted in Figure 1 b. The study was performed without noise or other sources of disturbance in order to evaluate its general potential.

A phase map was used to initialize the state of the tissue. The map was created by setting multiple phase singularities onto the tissue and distributing phase values equally on surrounding circles. Phase values for the remaining vertices were then interpolated with the Laplace scheme in several iterations. Finally, the curvature of the phase distribution was improved by the Eikonal approach [8]. Mapping the resulting phase distribution to cellular states served as initial input for the bidomain solver.

### 2.4 Cycle length analysis

The determination of CLs is essential for this study as the mean minimal CL observed for a region was used as a surrogate of the ERP of the underlying cells. LATs were defined
by two criteria for TMVs: Points at which the TMV exceeded -40 mV and its temporal derivative exhibited a local maximum within a time window of 5 ms were annotated as LATs. For EGMs, the LATs were calculated as maxima of the derivative. For both kinds of signal, a time lock of 40 ms prevented the erroneous detection of two LATs in a row. CLs were calculated as differences between subsequent LATs. Finally, the threshold based separability of area 1 and 2 by the minimal CL was quantified using the area under the curve (AUC) of the receiver operating characteristic (ROC). An AUC equal to 1 corresponds to perfectly separable classes whereas the classes overlap completely for an AUC of 0.5.

3 Results

3.1 Properties of the introduced cell membrane models

The ERP for different BCLs of pacing is given for the five levels of remodeling as well as for the original CRN model in Figure 3. Cells with stronger remodeling were capable of maintaining short BCLs down to 100 ms, whereas cells of the original CRN model stopped passing on excitation for BCLs lower than 330 ms. For each of the cell membrane models, the ERP depended on the BCL. However, the dependency diminished with the intensity of remodeling. ERPs of cells with a higher level of remodeling were consistently shorter than ERPs of cells with less remodeling. The intracellular conductivities yielding a CV of $\frac{300 \text{ mm}}{\text{s}}$ were [0.076; 0.078; 0.081; 0.086; 0.091] $\frac{\text{S}}{\text{m}}$ for remodeling levels 1 to 5.

3.2 Annotation of LATs

25,581 vertices of the model were located at the bath tissue boundary. LATs were determined in TMVs and EGMs for those vertices in each of the 30 simulation setups. 0.25 % of the activations determined in TMVs were missed in the EGMs and 0.31 % were detected erroneously. The mean absolute deviation between the activations found in both sources was 0.24 ms for an output time resolution of 1 ms. The following steps were performed with TMVs only as the LATs extracted from TMVs and EGMs were in good agreement.

3.3 Cycle length as an indicator for ERP

Figure 4 summarizes the findings from the comparison of minimal measured CLs to the ERP of the underlying cells for varying radius of the region of deviating substrate properties and different combinations of cell membrane models in signals of 2 s length. Standard deviation and mean minimal CL were calculated by taking the LATs of all vertices within the respective area as input.

The discrimination between area 1 and area 2 was dependent on two factors: First, a larger absolute difference in ERPs between the underlying cell membrane models favored the distinguishability. Figure 4 hardly shows a difference in minimal CL for setups combining remodeling levels 1 and 2. The discrimination worked best for the setups combining remodeling levels 1 and 4 as the absolute difference in ERP was larger than for any other of the tested combinations (see Figure 3). Second, larger regions were more easily distinguished. Larger areas were more likely to harbor an AFib driver and thus making full use of the minimal possible CL. Small areas did not provide a sufficiently large substrate to sustain a driver. Therefore, the observed CL depended on the frequency and complexity of activation in the surrounding tissue. As a result, regions of distinct substrate properties needed to exceed a minimum size for their successful identification. Figure 4 demonstrates this effect for example in the setups with remodeling levels 3 and 4 for diameters of 9 mm and 15 mm. The respective AUCs of the ROC verified these findings.

4 Discussion

We have proposed that one can overcome the sample density challenges of AFib mapping by measuring time independent
Figure 4: Minimal CLs for 30 geometric setups with areas of varying underlying ERP. Red dots and bars refer to the minimal CLs calculated from TMVs in area 1 (see Figure 1). Blue crosses and bars refer to area 2. The marker determines the minimal CL averaged over all vertices within the respective region. The bar depicts the standard deviation. Each bar is accompanied by a black line which marks the range of the ERP for the underlying cell model from the shortest possible BCL to a BCL of 1 s (see Figure 3). The five columns corresponding to each diameter of area 2 represent the following compositions of remodeling levels in area 1 and 2 from left to right: {lev1 - lev2}, {lev1 - lev3}, {lev1 - lev4}, {lev3 - lev4}, {lev3 - lev5}. The ROC AUC of each setup is shown at the bottom.

Making use of the minimal CL particularly stands out for being capable of dealing with partially disturbed signals. Unorganized electrogram segments can be discarded without an influence on the minimal CL, whereas unsteady signals would affect most frequency domain approaches. Furthermore, the method is not dependent on user input parameters, as LAT detection algorithms are automatized. This ensures the objectivity of the results.

The minimal CL is expected to approximate the ERP more effectively during longer recorded sequences as the probability of capturing two subsequent activations with minimal gap grows with recording time. In contrast to other approaches which often suffer from rising complexity of excitation patterns, a highly chaotic pattern favors the method introduced here.

Theoretical considerations demand the minimal CL not to be shorter than the ERP. However, several minimal CLs fell below the ERP in Figure 4. As the ERP was determined in a planar wave scenario and not under fibrillatory conditions, the difference in the excitation pattern explains the deviations.

In conclusion, the suggested method appears to be feasible for clinical mapping procedures provided electrodes have a spatial resolution sufficient to produce organized electrograms. In this study we have shown that measurement of local minimum CL corresponds to local ERP. Regions of lowered ERP can be identified if the regions are large enough and the ERP deviates significantly from the surrounding tissue.

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References