Influence of Conduction Velocity Restitution Steepness on Atrial Fibrillation Vulnerability and Maintenance

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Abstract

Atrial fibrillation (AF) is a public health burden with increasing incidence. Reentry events are drivers of AF, and investigation of their underlying mechanisms is ongoing. The influence of the conduction velocity (CV) on reentry events has been thoroughly studied in contrast to CV restitution. We simulated electrical wave propagation with the diffusion reaction eikonal alternant model (DREAM) in tissue slabs. Scenarios with combinations of three maximal longitudinal CV (CV_0) values (200, 400, and 600 mm/s) and 12 CV restitution curve morphologies extracted from electrode measurements in 13 patients with persistent AF, resulting in 36 experiments, were considered. In each experiment, an S1-S2 protocol was applied to induce reentry. The vulnerable window and average duration of reentries of each experiment were compared based on the steepness of the CV restitution. The vulnerable window increased with decreasing steepness of the CV restitution curve. The maximum increase was 59.6, 40.8, and 22.8 % for the three CV values, respectively. Similarly, for the average duration of reentries, a maximum increase of 38.6, 72.5 and 22.8 % was observed for less steep CV restitution. In conclusion, shallow CV restitution curves are characteristic of more vulnerable tissue and can contribute to maintenance of longer AF episodes.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an increasing incidence [1]. Patients face a higher risk for stroke [2], myocardial infarction [3] and mortality [4]. The treatment of AF is often insufficient, causing high recurrence rates [5] due to a lack of knowledge about the underlying mechanisms of AF [6]. Therefore, a better understanding of these mechanisms could improve the treatment outcome.

The conduction velocity (CV) is a well known factor influencing reentry events. Particularly, slow CVs advocate reentry events [7, 8]. Furthermore, it was demonstrated that reduced CV and broadened CV restitution are associated with fibroblast-myocyte coupling, prompting discordant action potential duration alternans [9], which increases the dispersion of refractoriness [10] and therefore increases the tissue's vulnerability to AF.

The objective of this work was to analyze the role of the CV restitution curve in reentry events to gain a better understanding and potentially improve the treatment of AF.

2. Methods

Data of 13 patients (8 female) with persistent AF and an average age of 67±8 years were used in this work. All participants provided written informed consent and the study was approved by the Institutional Review Board. A decremental pacing protocol was performed at Städtisches Klinikum Karlsruhe, with pacing cycle lengths (PCLs) ranging from 600 ms down to 180 ms. Initially, intervals were decreased by 50 ms. Upon reaching a PCL of 300 ms, the decrements were set to 10 ms. The pacing was stopped when AF was induced, providing an approximate last propagating PCL, denoted by j in the following. The time between the pacing stimulus and the detection of the depolarization wave at another location with a mapping catheter, also called post-pacing interval, was measured to derive CV restitution.

The electrophysiological simulations in this work were performed using openCARP [11] and the carputils framework.

2.1. CV Restitution Curve

The CV restitution curve was described by a continuous function depending on the PCL [12]:

$$CV_{\mathrm{PCL}} = \begin{cases} \mathrm{CV}_0 \left(1 - \mathrm{p} \cdot \mathrm{e}^{-(\mathrm{PCL}+\mathrm{k})\frac{\log(\mathrm{p})}{67\ \mathrm{ms}}}\right) & \text{for PCL} \geq j \\ 0 & \text{for PCL} < j \end{cases} \quad (1)$$

This equation was chosen due to its simplicity and interpretable parameters. The steepness of the curve is controlled by the parameter p. The term $log(p)$ in the exponential function additionally controls the point at which the decay of the CV starts. To minimize the number of variables, $log(p)$ was used to maintain the same parameter range for both usages of p, instead of introducing another variable. The shift along the PCL-axis is controlled by the parameter k. Initial fitting of the clinically measured CV restitution curves leads to the absolute value in the denominator of the exponential term. When the PCL is smaller than j, the wave will not propagate and the CV therefore drops to zero.

2.2. Clinically Measured Parameters

To acquire all values of p and k from the clinical data, the measured CV restitution curves of all electrodes of all patients were fit to equation 1. Values of p or k deviating more than three standard deviations from the median were considered outliers and excluded pairwise. A generalized linear mixed-effects model was applied to identify potential gender differences while accounting for multiple measurements of one patient. For p, the generalized extreme value distribution and for k the normal distribution were fitted to the 0.95 quantile of the histograms, respectively. The different distributions were chosen based on the distinct characteristics of the two parameters, with the best match to each distribution being utilized. The means and standard deviations of these distributions were then used to sample the combinations of p and k for the CV restitution curves used in the tissue slab simulations. The distributions were normalized to ensure a balanced influence of both parameters. The considered grid shown in figure 1 consists of the following values: μ_p, $\mu_p \pm std_p$, $\mu_p + 2std_p$, μ_k, $\mu_k \pm std_k$. The data points closest to the intersections with an available value for j were selected.

2.3. Tissue Slab Simulations

The triangular mesh for the tissue slab simulations had a size of $50\,\mathrm{mm} \times 50\,\mathrm{mm}$, with a spatial resolution of $dx = 0.8\,\mathrm{mm}$. Electrical wave propagation was simulated with the diffusion reaction eikonal alternant model (DREAM) [12, 13] and the Courtemanche ionic model [14]. To represent electrical remodeling due to AF, the conductance values of the Courtemanche model were modified according to Loewe et al. [15]. To furthermore personalize the ionic model, a function, see equation 2, interpolating between healthy ($x(j) = 0$) and AF conductance values ($x(j) = 1$), was utilized. With this function, the specific values of j were translated into conductance values $\vec{g}$.

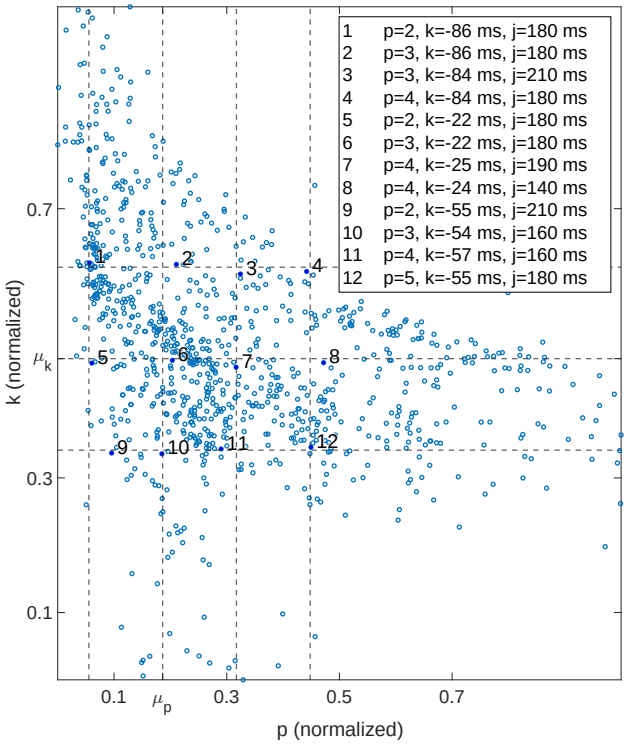

Figure 1. Clinical CV restitution curve parameters. Each data point represents a CV restitution curve measured at a specific electrode of a patient. The dotted lines indicate multiples of the standard deviations of the distributions of p and k and the filled dots indicate the chosen data points for the experiments. The corresponding parameters are listed in the top right corner.

$$\vec{g} = (1 - \mathrm{x(j)}) \cdot \tilde{\mathrm{g}}_{\mathrm{healthy}} + \mathrm{x(j)} \cdot \tilde{\mathrm{g}}_{\mathrm{AF}}, \mathrm{x(j)} \in [0, 1] \qquad (2)$$

Each experiment consisted of a fixed parameter set of p, k, j (see figure 1), and CV_0 for the whole mesh. An S1-S2 protocol was then used to initiate reentry. Five S1 stimuli were triggered at the left boundary of the tissue slab. At a specific time t_{S2}, the S2 stimulus was triggered in the left bottom corner enclosing one fourth of the mesh. Simulations were performed to identify all t_{S2} that induce reentry. All simulations for a set of p, k, j and CV_0 with the corresponding inducing t_{S2} build one experiment. The identification of all t_{S2} was automated by detecting if the wave evolving from the S2 stimulus was blocked, propagated normally, or induced a reentry.

2.4. Vulnerability Assessment

To assess the effect of the CV restitution on AF vulnerability and maintenance, the vulnerable window and the average duration of reentries were analyzed. The vulnerable window was calculated by subtracting the earliest t_{S2} that

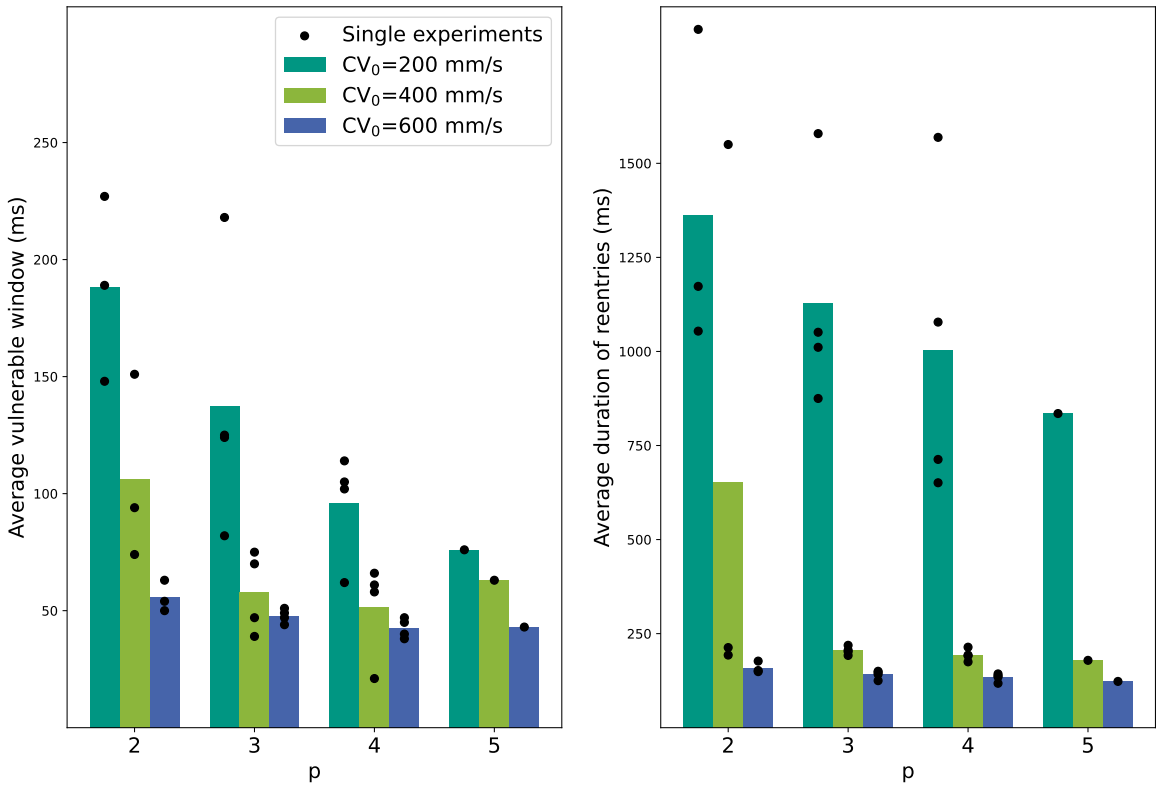

Figure 2. Results of tissue slab simulations. On the left, the average vulnerable window is shown for the different values of p. As the value of p increases, the CV restitution curve becomes steeper. Black dots represent the results for the single experiments with parameters p, k, j and CV_0. The bars represent the average value of the experiment results with the specific value of p, j, CV_0 and the different values of k. The three colors represent the different CV_0 values that were used. On the right, the same is shown for the average duration of reentries.

induced reentry from the latest t_{S2}. The duration of each reentry episode was calculated by subtracting t_{S2} from the latest activation time of the simulation. Averaging all reentry durations of one experiment gave the average duration of reentries. The vulnerable window and the average duration of reentries were analyzed regarding the steepness of the CV restitution curve corresponding to the parameter p.

3. Results

A potential gender effect was ruled out by the generalized linear mixed-effects model. Figure 2 shows the results for the average duration of reentries and the vulnerable window of all experiments. The vulnerable window and the average duration of reentries increased with decreasing CV restitution steepness (p) for all CV_0 values, except for the average vulnerable window for $p = 5$ and $\mathrm{CV}_0 = 400\,\mathrm{mm/s}$. Moreover, all values increased with decreasing CV_0 value. The effect of p was most prominent for $\mathrm{CV}_0 = 200\,\mathrm{mm/s}$.

In total, the maximum increase in the average vulnerable window (value at $p = 5$ compared to $p = 2$) was 59.6, 40.8, and 22.8 % for the CV_0 values of 200, 400 and 600 mm/s, respectively. Likewise, the average duration of reentries increased by a maximum of 38.6, 72.5 and 22.8 %.

4. Discussion

The observed behavior of increasing average vulnerable window and duration of reentries with decreasing CV_0 value was expected, since slower CVs are known to cause higher vulnerability and longer AF maintenance [7].

The increasing average vulnerable window with increasing p can be explained by the tissue having a broader range of PCLs for which restitution is present in a more shallow curve. Consequently, more PCLs slow down the wave without blocking it, making a more shallow curve more vulnerable regarding t_{S2}. Therefore, with a shallow CV restitution, ectopic foci are more likely to induce reentry events because of a greater width of the vulnerable window. Hence, reentry events are prone to occur more fre-

quently.

Similarly, longer average duration of reentries with shallow CV restitution can be explained by restitution causing slower wave propagation and therefore reentries that are more likely to hit excitable tissue and be sustained. Shallow CV restitution therefore leads to longer maintenance of reentries. The relationship between CV restitution steepness and the duration of reentries observed in the tissue slab experiments suggests a potential influence of CV restitution on the maintenance of AF. Consequently, a shallow curve not only leads to a higher probability of reentry events but also to longer lasting AF episodes, increasing patient burden causing progressive tissue remodeling, and increasing risks for comorbidities like stroke [16].

The simulations conducted in this work simplify human atrial electrophysiology to a certain extent: Firstly, the simulations were conducted in homogeneous 2D tissue slabs with homogeneous CV. Secondly, the DREAM is currently not considering source-sink balance effects. However, all simulations are affected by these limitations, rendering their effects negligible for this work.

Nevertheless, the findings of this work have translational potential. Firstly, in drug development, the shape of the CV restitution curve could be considered and targeted. Secondly, a clinical protocol could be introduced that measures the CV restitution to use this information for ablation planning.

5. Conclusion

In summary, we found that a shallow CV restitution curve favors vulnerability to and maintenance of AF.

Thus, the steepness of the CV restitution curve is a crucial factor for reentry events and should undergo further investigation. The shape of the CV restitution curve can potentially be modified by drugs, opening new approaches in AF therapy.

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