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The APD Restitution Hypothesis Revised: Slope >1 Does Not Always Determine Alternans and Spiral Wave Breakup

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Background: Action potential duration (APD) restitution relates the duration of an AP to previous activations. Over the last decade many numerical studies have shown that APD restitution can be used as a predictor for alternans and stability of spiral waves. It has been shown using iterative maps and numerical simulations of simple ionic models that if the slope of the restitution curve is > 1, alternans will be present and spiral waves will break into multiples, a mechanism that has been associated with the transition from tachycardia to fibrillation. However, some experiments have reported steady state APD restitutions with slope >1 without alternans in APD. Methods: By including a history of previous activations (memory) in the iterative maps as well as using more complex ionic models with such memory, it can be shown that under certain conditions even when slope $\gg$1 neither alternans nor spiral wave breakup are present. Furthermore, independent of memory, an analysis of electrotonic effects on the wave back also can reveal whether alternans will occur. Results: We present simulations of ionic models in which despite APD restitution slope $\gg$ 1, no alternans is present at any period of stimulation due to memory and spiral waves rotate without breakup. We also show that even when there is no memory, electrotonic effects alone can stabilize a train of waves and prevent alternans in an ionic model with slope $\gg$1. This occurs when at least part of the repolarizing wave back is relatively fast and the conduction velocity restitution is shallow. In these cases alternans is present in single cells but not in 1D rings or in spiral waves. Conclusions: Two scenarios can explain experimental results of no alternans even when the slope of the APD restitution curve is >1: memory of previous activations and electrotonic effects. We have demonstrated that these two effects in ionic models can prevent alternans and spiral wave breakup.

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Role of Vagal Stimulation in Atrial Fibrillation

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Action potential duration (APD) heterogeneity is a known factor in promoting breakdown of atrial flutter into fibrillation. Due to discrete nerve endings, vagal stimulation produces a nonuniform [ACh] which leads to APD dispersion. The purpose of this study was to elucidate the role of this dispersion in the breakdown of flutter into fibrillation. A morphologically realistic computer model of the canine atria, with a detailed ionic description, was used to ascertain how both the size of ACh release sites and [ACh] affected an induced reentry. Identical islands, signifying ACh release sites, were uniformly distributed. Diameters of 1.6, 2.4 and 3.2 mm were simulated. The number of islands was increased as the size was decreased to conserve overall area. Concentratons of ACh ranged from 0 to 3 nmol/L which yielded APD's of 200 to 80 ms respectively. All islands were assigned the same [ACh] while [ACh] outside of the islands, referred to as the basal level, was varied independently with the constraint that it was lower than or equal to the island [ACh]. Results were consistent for all island sizes: small differences in [ACh] between the basal and island levels produced reentry that tended to be stable, and, for low [ACh], was a simple rotor anchored around some anatomical feature. In the left atrium, this was a pulmonary vein while in the right atrium, this was either the SVC or IVC. Increasing [ACh], while still maintaining a small difference between the regions, led to formation of macro circuits utilizing the coronary sinus sheath. A further increase resulted in stable figure-of-8 reentry. Conversely, with large [ACh] differences, wavebreaks started to occur. With the smallest-sized islands, there was little noticable breakup. For the largest island size, more wavelets were present since the wavefront started to turn back on itself by the time it had traversed the island. In conclusion, the geometry of the atria restrict the reentrant pathways which may form. A high degree of APD dispersion is needed for breakup to occur. An overall decrease in wavelength will not result in more wavefronts but will allow reentries which do not have to anchor around obstacles. The fibrillation observed was more typical of a mother wavelet.

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Optimization of Antitachycardia Pacing Using a Computer Model of Atrial Arrhythmias

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Introduction: Many mechanisms underlying initiation, perpetuation and termination of atrial fibrillation still remain unclear. To better understand antitachycardia pacing techniques, a computer model of human atria was developed. This model allows us to study and optimize pacing termination of atrial arrhythmias. Method and Results: A computer model of human atria with an anatomical structure based on human MR images has been developed. The cellular model used reproduces atrial restitution properties. Unipolar and bipolar electrograms can be calculated simultaneously at any point on the atrial surface, providing a link to clinical data. Measures of the degree of organization in the atrial tissue have also been implemented. Different types of atrial arrhythmias have been induced in this model using rapid pacing. Sustained AF was obtained by clinically relevant stimulation protocols and maintained over longer periods by electrical remodeling of the atrial cells. Given a sustained arrhythmia, different pacing algorithms have been applied to terminate it. The effect of pacing site and interval has been studied. Our simulation studies confirm that typical atrial flutter can be terminated by rapid pacing of the isthmus. We also observed that more complex arrhythmia can in some cases be controlled, depending on the timing, location and frequency of pacing. Our simulations show that the best control of the atrial arrhythmia is obtained when pacing is done at the anterior wall of the right atrium. Conclusion: This atrial model may serve as a tool to obtain a better understanding of the mechanisms of antitachycardia pacing techniques, in particular for more complex techniques such as multi-site pacing. Some of its advantage is the possibility to access easily different sites of pacing and to reproduce many experiments with different parameters.

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Temporal Excitable GAP During Fibrillation Is Dependent on Fiber Orientation Due to Anode-Break Excitation

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Background: Recent studies have demonstrated capture during cardiac fibrillation. It is typically assumed that the temporal excitable gap (capture window) during fibrillation reflects the size of the spatial excitable gap. The aim of the present study was to evaluate numerically the validity of this concept. Methods: Simulations of a single spiral wave (SW) were conducted on a homogeneous bidomain sheet (3.75 × 1.5 cm) incorporating parallel fiber orientation. Based on previous experiments, which reported that the capture threshold was above 5x diastolic pacing threshold, a 20-mA point stimulus (4 ms, unipolar, cathode) was delivered externally (electrode positions: black dots in figure). Capture ratio (the ratio of capture window to SW cycle length) was measured at each electrode position. Results: The distribution of the capture ratio is shown with the white curved lines in the left panel. The distribution was not parallel to the fiber direction. Outside the SW core, the areas diagonally adjacent to the core showed a high capture ratio due to the formation of two virtual anodes in the direction of the fibers during the stimulus (see right panel). At least one of them recovered the excitability of the SW arm. Therefore, when the stimulation site was located diagonally with respect to the core (upper left or lower right in case the SW rotates counterclockwise), the anode-break excitation wavefront easily invaded the spatial excitable gap, resulting in a successful capture. Conclusions: The fiber orientation, which determines the anode-break excitation spatial pattern, *can influence* the temporal excitable gap during SW reentry. Consequently, the distribution of the temporal excitable gap does not directly reflect the spatial excitable gap.