Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Action Potential Duration Gradient Protects the Right Atrium from Fibrillating

Marc Ridler, David M. McQueen, Charles S. Peskin, and Edward Vigmond

Abstract— **Atrial Fibrillation (AF) is the most common cardiac arrhythmia. It is characterized by rapid and disorganized electrical activity in the atria. Atrial arrhythmias can be triggered from an ectopic focus, i.e., an abnormal impulse originating in an area other than the sinus node, generating reentrant waves. The regional ionic heterogeneities found in the atria cause a gradual shortening of the action potential duration (APD) with increased distance from the sinoatrial node. It is generally thought that the only electrophysiological consequence of the spatial dispersion of cardiac action potentials (AP) is the enhancement of reentry. This paper investigates the effect of a gradient in APD on arrhythmogenesis via computer simulations.**

A gradient of ionic properties was introduced into a computationally efficient computer model of the canine atria to produce a smooth distribution of APDs. The window of vulnerability for ectopic beat-induction of reentry was determined for both left atrium (LA) and the right atrium (RA) stimulation, with and without an APD gradient.

The shortened windows of vulnerability in the RA, due to the addition of the APD gradient, suggests a protective mechanism against AF. The left atrial window of vulnerability was slightly longer from ionic dispersion.

I. INTRODUCTION

Atrial arrhythmias, in particular atrial fibrillation (AF), are the most prevalent cardiac arrhythmias. While not directly lethal, AF increases the risk of stroke, can impair cardiac function, and can interfere with quality of life [1]. Atrial arrhythmias can arise from ectopic foci that establish one or more reentrant waves (reentry). Certain conditions predispose the atria to form reentrant waves: shorter action potential durations (APD) and sharp APD heterogeneity [2]. Short APDs ease the ability of re-entrant circuits to form and perpetuate themselves. Sharp APD heterogeneity between regions, such as islands of acetylcholine (ACh) release, can act as anchors for reentrant wavefronts to develop, as well as lead to wavebreak [3]. It is generally thought that the only electrophysiological consequence of spatial dispersion of cardiac action potentials (AP) is the enhancement of reentry [4].

This work was not supported by any organization

M. Ridler and E. Vigmond are with the Faculty of Electrical Engineering, University of Calgary, 2500, University Drive, N.W., Calgary, Alberta, Canada, T2N 1N4 mridler@ucalgary.ca

Peskin and McQueen with the Courant Institute of Mathematical Sciences New York University, 251 Mercer Street, New York, N.Y. 10012-1185

CT scan images used in constructing the atrial model were provided by Arthur E. Stillman, M.D., Ph.D., and Randolph M. Setser, D.Sc. at The Cleveland Clinic Foundation, Cleveland, Ohio; and invaluable assistance in the use of these images was provided Thomas O'Donnell Ph.D., Siemens Corporate Research, Princeton, New Jersey.

An intrinsic property of the canine atria is a progressive shortening of APD with increased distance from the sinoatrial (SA) node [4]. Within the right atrium (RA) alone, multiple differences in AP shape and duration exist between regions [4], [5], [6]. Between the two atria, APD is shorter in the LA versus the RA in both isolated cells and multicellular preparations, and the effective refractory period (ERP) is shorter in the left atria (LA) compared with the RA in vivo [7], [8]. The ionic mechanism driving the spatial decrease in APD within the canine RA is attributed to decreasing calcium L-type current ($I_{Ca,L}$) and increasing rapid-potassium current (I_{Kr}) [5]. Between the two atria, the LA myocytes exhibit larger I_{Kr} than do RA myocytes, producing shorter APDs and ERPs [7]. Larger I_{Kr} has been cited to participate in the ability of the LA to act as a "driver regions" for AF, further aided by sharp ionic heterogeneity in the pulmonary vein (PV) vicinity [7] .

We use a computer model, based on a previously described morphologically accurate model [9] of the canine atria, to ascertain the effects of an APD gradient on atrial arrhythmogenesis. We will show for the first time that the RA window of vulnerability to ectopic foci is reduced with the addition of an APD gradient. Development of a pharmacological enhancement of this naturally occurring protective mechanism may prove to be beneficial for AF sufferers.

II. METHODS

A. Atrial Model

Our previous work used a morphologically realistic 3D cable representation of the canine atria [9]. In this work, we produced a geometrically realistic model. Surfaces were constructed from computer-aided tomography data, and cables were generated by constructing geodescics on the surfaces. The model, like the previous, incorporated the relevant atrial anatomical features: physiologically based three-dimensional fiber orientation; anisotropic conductivity; openings for the major veins, atrioventricular valves, and the coronary sinus (CS); the conducting rim of the fossa ovalis; the conducting muscular sheath of the CS; and atrial walls with thickness. The model was constructed from a series of cables for reason of computational efficiency so that long times could be simulated with a finer degree of spatial discretization in the model. The model comprised 5,717 cables divided into 1,470,237 segments, each of length 100 μm, which were connected to each other by 773,305 junctions. Cable resistivity was increased, and the number of junctions reduced, to slow propagation velocity by a factor of two.

Solution to the system of equations followed the interconnected cable method previously developed [10]. Briefly, the method is a monodomain formulation that allows each muscle fiber to be treated separately. The cable equation is solved for each fiber, and then, by conserving current at junctions connecting fibers, individual fiber solutions are merged together, allowing reduction in system order and lending itself to parallel implementation. The resultant system of ordinary differential equations is solved with a time step of 25 μs.

B. Ionic Model and Gradient

Because the size of the model is close to that of the canine atria, the ionic current model chosen was the canine atrial action potential model by Ramirez et al. [11]. It consisted of 13 ionic currents with adjustable conductances to regulate rapid-potassium ($I_(Kr)$), transient-outward (I_{to}) and calcium L-type ($I_{Ca,L}$) currents. The AP morphology was altered by regulating these ionic currents.

An APD heterogeneity gradient was introduced in the model by evenly stepping the ionic conductances of $g_{Ca,L}$ from 0.6 to 0.4, g_{to} from 0.7 to 1 and g_{Kr} from 1 to 3, with respect to their normalized values measured in nS/pF, for a short to long APD. Thirty regions were defined in the model based on time of first activation after a sinoatrial node stimulus and, corresponding ionic conductances were assigned to each region.

C. Simulation Protocol

The ionic model was pre-paced for 15 sec at 1 Hz to achieve ionic equilibrium. Sinus-node activity was modeled by applying a 2 ms long transmembrane current stimulus to a cylindrical volume of tissue near the superior vena cava. Two areas in the atria were selected for the location of the S2 ectopic beat: the posterior wall of the LA close to the pulmonary veins, and the RA posterior wall. For both locations, the minimum S2 radius to initiate reentry in the homogeneous model was determined by applying a 1 ms long transmembrane ectopic stimulus during recovery. The window of vulnerability was subsequently determined for both locations. Ionic gradient was applied to the model, keeping all other parameters constant. Again, the window of vulnerability was found for both locations.

D. Data Analysis

Only single rotor, figure-of-eight functional reentry was analyzed. The window of vulnerability was defined as the difference between the shortest and the longest S1-S2 interval for which reentry was induced. The maximum temporal resolution used to search for reentry was 0.2 ms.

III. RESULTS

A. Reentry

Total time for the 4 cm model to activate from the sinus beat was 260 ms for both the homogeneous and APD gradient model. (Fig.2) The minimum ectopic radius to elicit

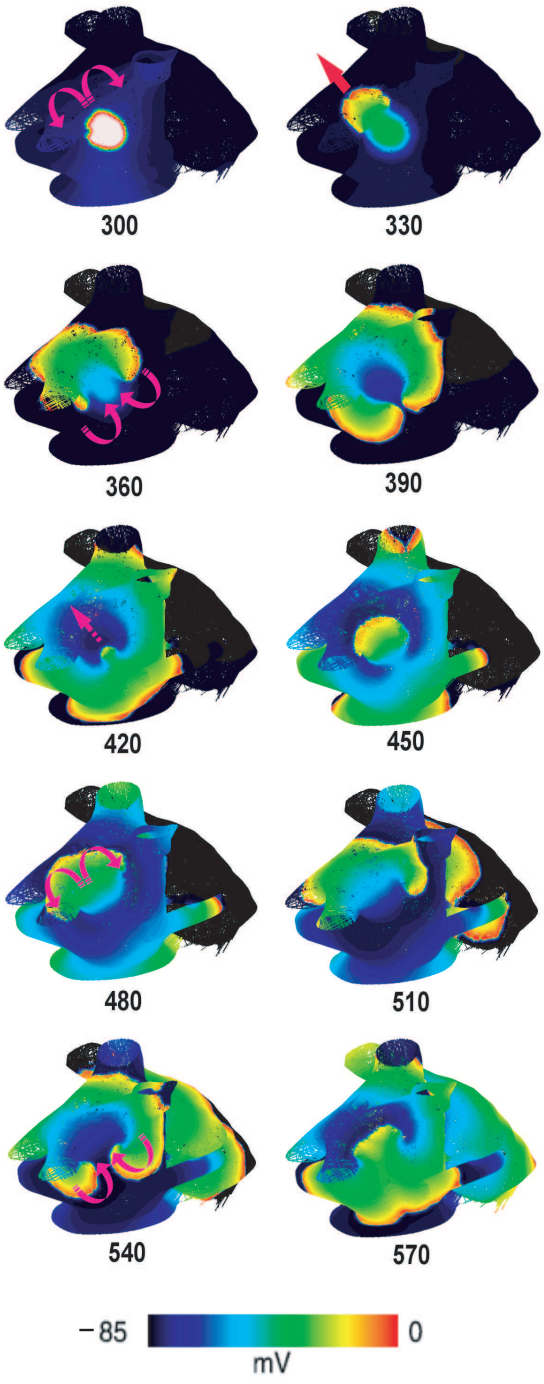

Fig. 1. Reentry in a homogeneous atrial model (time in ms). The ectopic stimulus (S2) at time 300ms after the sinus stimulus (S1) generates a figure-of-eight reentry pattern (represented by the purple arrows). The S2 is located on the posterior wall of the LA. The propagating wavefront reenters the ectopic area twice at time 450 and 570 ms. The initial direction of the propagating wavefront (red arrow at time 330 ms) is towards tissue most repoloarized. In this homogeneous time series, the area most repoloarized is the tissue that was earliest activated from the S1.

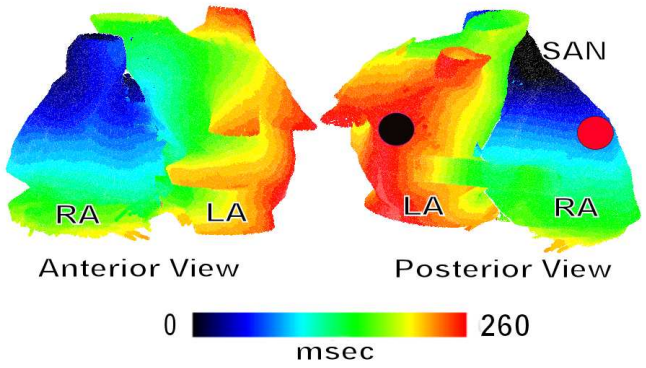

Fig. 2. Time activation map during sinus rhythm. The atria is spatially discritized into 30 regions based on time of first activation. The locations of the ectopic beats are marked by a red dot in the RA and a black dot in the LA. The SA node (SAN) in the RA generates the stimulus for regular sinus rhythm (S1) and is therefore the first area to activate at time 0. The last area activated is the left atrial free wall (red area best seen in the posterior view.

reentry varied between the two locations: 8.68 mm in the LA and 11.57 mm in the RA. Figure-of-eight reentry was obtained by applying an ectopic stimulus (S2) during the window of vulnerability (see Fig. 1).

Reentry arose from abnormal impulse propagation between different zones of tissue within an ectopic stimulus area. The initial wavefront formation depended on tissues being in different repolarized states when the ectopic foci occurred. The zone most repolarized would activate and generate an outward propagating wavefront, whereas no AP would be elicited in tissue not sufficiently repolarized. The propagating direction of the initial wavefront was towards tissue most repolarized. See red arrow Fig: 1. Therefore towards the sinus rhythm generating SA node. Duration of a single figure-of-eight reentry took around 150 ms.

B. Ionic Dispersion

The coupled and intrinsic; long, short and homogeneous action potentials are shown in Fig: 3. The amplitude of the AP was reduced and the APD shorter when electrotonically coupled in the model. The ectopic locations chosen were close to the SA node in the RA and distal to the SA node in the LA. The coupled APs at those locations were therefore close to the coupled APs within the whole atria.

C. Window of Vulnerability

Results for the duration of the window of vulnerability for two ectopic locations for both a homogeneous and APD gradient model, are summarized [Table I]. The RA window of vulnerability was greatly reduced by over a factor of two with an applied gradient. Conversely, the LA window was slightly larger.

IV. DISCUSSION

This study ascertained the effect of an APD gradient on arrhythmogenesis in a geometrically realistic atrial computer model. The window of vulnerability for an ectopic beat

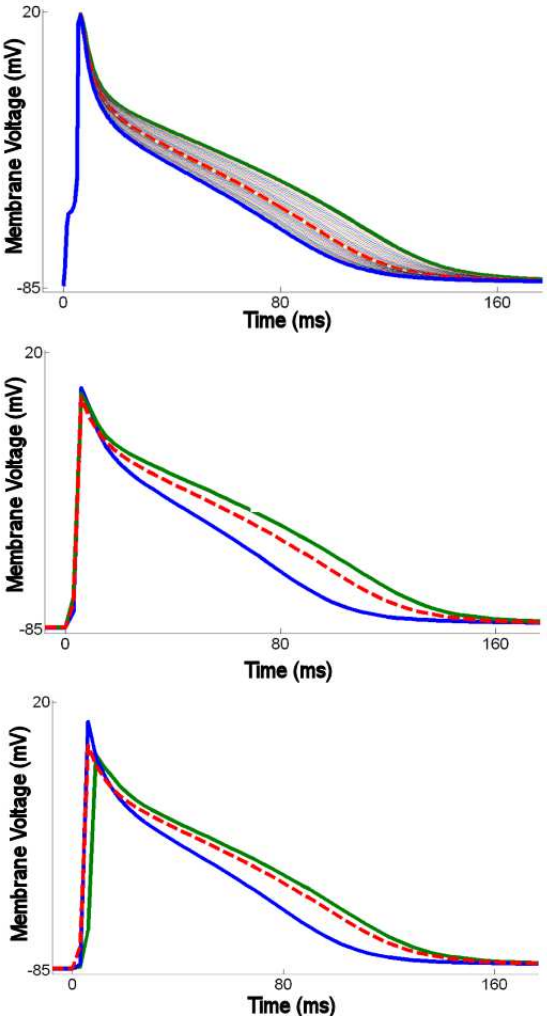

Fig. 3. Top: Intrinsic AP gradient of prepaced isolated cells. Longest (green) and shortest (blue) APDs were assigned to regions with the latest and earliest time-to-activation respectively. Intermediate APs were assigned to atrial regions based on time of first activation. The homogeneous AP (red-dashed) represents mid ionic conductances. Middle: Effect of electrotonic coupling. The magnitude of the AP gradient diminished slightly from 33 ms for intrinsic APs to 30 ms for electrotonically coupled APs. Bottom: Coupled APs at the center of the ectopic sites. The AP of the LA ectopic site (blue) is markedly shorter than the homogeneous AP (red-dashed), whereas the AP of the RA ectopic site (green) is slightly longer.

TABLE I
TIME WINDOW OF VULNERABILITY - HOMOGENEOUS AND APD GRADIENT MODEL

	Window of Vulnerability (ms)	
Ectopic Location	Homogeneous	Gradient
RA	4.2	2.0
LA	2.2	2.4

was determined for both a control homogeneous model, and a model with a spatial APD gradient. We found that the window of vulnerability in the RA was narrower with an applied gradient, while slightly wider in the LA, when compared to the homogeneous case.

A. Reentry

Current reentry theories broadly conclude that ionic heterogeneity and shortened APDs promote AF. This paper presents a particular case where these factors prove to be protective. The ionic gradient introduced, hindered the forward progress of an AP wavefront because its initial path towards the SA node led to tissue with longer APDs. With a gradient applied, that tissue was proportionately less repolarized. This effect occurred at both ectopic locations. The LA ectopic location was chosen at a point distal to the SA node where the APD is shortest. From the bottom of Fig. 3, the coupled APD at the ectopic site was markedly shorter than the coupled homogeneous APD. In homogeneous conditions, shorter APDs would result in a significantly increased window of vulnerability. With the gradient applied, the window of vulnerability was only 0.2 ms longer. In the RA as well, the gradient had a protective effect. Despite a slight increase in APD (bottom of Fig. 3) with respect to the homogeneous APD, the window of vulnerability was reduced by over a factor of two, from 4.2 ms to 2 ms.

B. Ionic Gradient

Little data is available quantifying the ionic mechanisms driving the AP gradient in canines. Feng et al. recorded APDs in the RA ranging from, 270 ms in the crista terminalis, to 160 ms in the atrioventricular ring, due to a 63% decrease in $I_{Ca,L}$ and 61% increase in I_{Kr}. The APD in the pectinate muscle was measured to be 180 ms driven by a 57% decrease in I_{to} [5] alone. These data suggest the existence of distinct structures within the RA. Across the right and left, Li et al. measured differences in ionic currents. They found a 33 ms decrease in APD and a 60% increase in I_{Kr} [7].

Our model uniformly stepped ionic conductances to achieve a smooth intrinsic APD gradient of 33 ms across the atria in best accordance with the data available. Only one gradient magnitude was examined in this study. A greater gradient would result in much longer APDs in the RA, further protecting that tissue. In the LA, the APD would be further shortened. An optimal gradient might exist whereby the atria is most protected from reentry.

This study looked at single figure-of-eight reentry. Different types of reentry, such as single rotor, anatomical macro-reentry and quasi-stable circuits, may result from varying the APD gradient magnitude. Longer simulations would be required to evaluate the progression of flutter into AF.

C. Limitations

Due to the size and complexity of our canine model, only single figure-of-eight simulations were feasible to complete in tractable time. Longer simulations would provide greater insight into arrhythmogenesis versus ionic dispersion. The exact ionic mechanism underlying the APD gradient remains elusive. The few studies done looking into the ionic currents driving APD gradients in the canine atria are incomplete. Feng et al. accounts for the ionic dispersion in the RA from the variance in $I_{Ca,L}$, I_{to} and I_{Kr} [5] whereas Li et al. only to I_{Kr} between the LA and the RA [7]. It is reasonable to suppose additional currents are involved in shaping AP morphology in tissue not previously examined.

V. CONCLUSION

An ionic gradient was applied to a computationally efficient canine model to ascertain the arrhythmogenic effect of the gradual shortening of APD with increased distance from the SA node. The window of vulnerability from an ectopic foci, is shorter in the RA, but not in the LA, with an applied gradient when compared to homogeneous AP distribution. The APD gradient interrupts initial ectopic waves from propagating due to regions with longer refractory time.

REFERENCES

[1] W. Kannel, R Abbot, D. Savage and P. McNamara, Epidemiologic Features of Chronic Atrial Fibrillation: The Framingham Study, *J. Med.*, vol. 306, 1982, pp. 1018-1022.

[2] S. Nattel, New Ideas About Atrial Fibrillation 50 Years On, *Nature*, Vol. 415, 2002, pp. 219-226.

[3] E.J. Vigmond, V. Tsoi, S. Kuo, H. Arevalo, J. Kneller, S. Nattel and N. Trayanova, The Effect of Vagally Induced Dispersion of Action Potential Duration on Atrial Arrhythmogenesis, *Heart Rhythm*, Vol. 1, No. 3, 2004, pp. 334-344.

[4] M. Spach, P. Dolber, and J.F. Heidlage, Interaction of Inhomogeneities of Repolarization With Anisotropic Propagation in Dog Atria, *Circ. Research*, vol. 65, No. 6, 1989, pp. 1612-1631.

[5] J. Feng, L. Yue, Z. Wang and S. Nattel, Ionic Mechanisms of Regional Action Potential Heterogeneity in the Canine Right Atrium, *Circ. Res.*, Vol. 83, 1998, pp. 541-551.

[6] A. Burashnikov, S. Mannava and C. Antzelevitch, Transmembrane Action Potential Heterogeneity in the Canine Isolated Arterially Perfused Right Atrium: Effect of IKr and IKur/Ito Block, *AJP-Heart Circ. Physiol.*, Vol. 286, 2004, pp. 2393-2400.

[7] D. Li, L. Zhang, J. Kneller and S. Nattel, Potential Ionic Mechanisms for Repolarization Differences Between Canine Right and Left Atrium, *Circ. Res.*, Vol. 88, 2001, pp. 1168-1175.

[8] S. Lee et al., Regional Differences in the Recovery Course of Tachycardia-Induced Changes of Atrial Electrophysiological Properties, *Circulation*, Vol. 99, 1999, pp. 1255-1264.

[9] E. Vigmond, R. Ruckdeschel and N. Trayanova, Reentry in a Morphologically Realistic Atrial Model, *J. Cardiovasc. Electrophysiol.*, Vol 12, 2001, pp. 1046-1054.

[10] J. Leon and F. Roberge, Structural Complexity Effects on Transverse Propagation in a Two-Dimensional Model of Myocardium, *IEEE Trans. Biomed. Eng.*, Vol 38, 1991, pp. 997-1009.

[11] R. Ramirez, S. Nattel, and M. Courtemanche, Mathematical Analysis of Canine Atrial Action Potentials: Rate, Regional Factors, and Electrical Remodeling, *Am. J. Physiol.*, Vol. 279, 2000, H1767-H1785.