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Implication of the inferior vena cava in the generation of reentry in the pectinate muscles

Implicación de la vena cava inferior en la generación de reentradas en los músculos pectíneos

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence increases with age. The most dangerous and complex arrhythmias are the result of a phenomenon known as reentry. In experimental studies, the vena cava has been associated with ectopic activity that promotes the generation of reentries. The changes caused by electrical remodeling in an atrial myocyte action potential model (AP), coupled with an anatomically realistic three-dimensional model of human atria with orientation fibers were incorporated in this work. When applying an ectopic focus to the nearby ostium of the inferior vena cava, a relationship between this activity and the generation of reentries in the pectinate muscles is found. A functional reentry repeated in time is favored by the pectinate muscles anatomy, the anisotropic properties and the non-uniform distribution in the three-dimensional tissue. The existence of a preferential conduction pathway facilitates the initiation of reentries affecting the conduction scheme. Therefore, the capacity of induction and development of arrhythmias are found.

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----------Keywords: Pectinate muscles, inferior vena cava, anisotropic, atrial arrhythmia, reentry

Resumen

La fibrilación auricular (FA) es la más común de la arritmia cardiaca y su prevalencia aumenta con la edad. Las arritmias cardiacas más peligrosas y complejas son el resultado del fenómeno conocido como reentrada. Se ha planteado que los músculos pectíneos proveen un sustrato para la actividad reentrante durante la FA. En estudios experimentales la vena cava ha sido asociada con actividad ectópica que promueve la generación de reentradas. En este trabajo se incorporaron los cambios generados por el remodelado eléctrico a un modelo de potencial de acción (PA) de miocito auricular, acoplado con un modelo tridimensional anatómicamente realista de aurícula humana con direccionamiento de fibras. Al aplicar un foco ectópico en la cercanía del ostium de la vena cava inferior se encuentra una relación entre esta actividad y la generación de reentradas en los músculos pectíneos. Una reentrada funcional que se repite en el tiempo es favorecida por la anatomía de los músculos pectíneos, las propiedades anisotrópicas y la distribución no uniforme en el tejido tridimensional. Se encontró la existencia de un camino de conducción preferencial que facilita la iniciación de reentradas afectando el esquema de conducción y la capacidad de inducción y desarrollo de arritmias.

----------*Palabras clave:* Músculos pectíneos, vena cava inferior, anisotropía, arritmia auricular, reentrada

Introduction

Obtaining accurate information about the formation and transmission of the cardiac impulse in normal and pathological conditions has permitted a better understanding of the mechanisms underlying cardiac arrhythmias [1]. The cardiac electrical activity models are theoretical schemes of electrophysiological phenomena based on mathematical models and help to facilitate the understanding and prediction of their behavior in various normal and pathological situations. Mathematical modeling and anatomical structures, along with computational simulation, contribute to the detailed analysis and comprehension of the source of reentries that give rise to the atrial arrhythmias of electrical origin since the complexity inherent to this phenomenon makes its study very difficult by using only the experimental approach.

In our work, we used a highly realistic (3D) computational model of the human atrium to which the orientation of fibers was added in order to analyze the characteristics and the wave propagation velocity of the action potential under the anisotropic effects of the tissue, and the curvature of the wave front. Our model involves fiber orientation, anisotropic conductivity and electrophysiological heterogeneity for different atrial tissues, which allow a higher-precision reproduction of the electrical behavior of the tissue under normal physiological conditions as well as under electrical remodeling, thus allowing a better analysis of the non-linear propagation dynamics in an excitable medium to understand heart diseases.

In this simulation study, we analyzed the way in which a complex atrial structure such as the pectinate muscles (PM) in remodeling condition

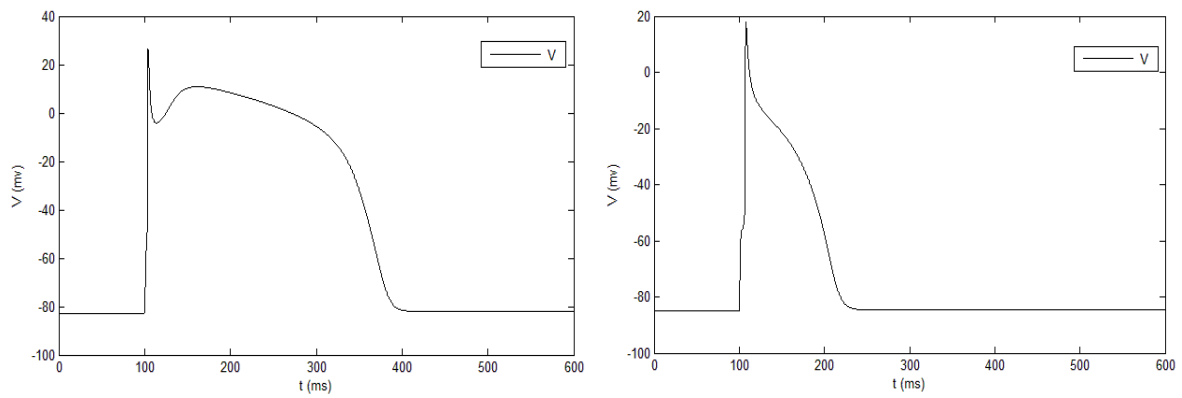
facilitates the generation of a reentry. In addition, the factors determining the spread of the cellular activation in the cardiac tissues [2] are studied, among which intercellular connections and the spatial arrangement of cardiac fibers are highlighted. Since propagation occurs within a multicellular environment whose properties are anisotropic, the orientation of cardiac fibers determines the manner of conduction in a structure such as the pectinate muscles in which propagation is preferably longitudinal. Several studies [3-5], have determined that PM play an important role in the generation and maintenance of reentry and have tried to relate them to the complexity and thickness of this anatomical structure. They conclude that the tissue local thickening observed in the PM facilitates the emergence of sustained circular reentry. The PM offer alternative ways that act as a bridge or as long range connections with a slightly faster conduction velocity giving rise to epicardial breakthrough patterns between different cardiac areas affecting the conduction scheme and therefore, the induction and evolution capacity of the arrhythmias.

Given that the vena cava has been implicated as a place of ectopic activity that initiates and perpetuates the atrial fibrillation, we have chosen this structure for its proximity to the PM to analyze its electrical behavior through simulation.

Methods

Electrical remodeling

The Courtemanche [6] cellular electrophysiology model for human atrial was implemented, which reproduces cellular electrical activity under physiological conditions; this model has 21 variables, expressions for 12 transmembrane currents and management of intracellular calcium. For electrical remodeling conditions, the model [7] developed by the same author was modified, and some changes were applied to the model parameters. Since we obtained a total repolarization time of 345 ms under normal conditions and an APD90 (AP 90% of repolarization) of 235 ms in tissue, the action potential duration (APD) of this model is extremely long and is due mainly to the maximum conductance value of the inward rectifier K^+ current (gk1=0.09 nS/pF.) This small value of gk1 yields a high-input membrane resistance (≈174 MΩ) [8]; this is why we modified this value increasing it 250% (gk1=0.225 nS/pF), placing it within the range of the measurements made by [9] in atrial cells. Also the maximum L-type Ca2 (gCaL=0.03714) current conductance was modified with a decrease of 70% of the control value; we modified the maximum transitory outward K+ current conductance with a decrease of 50% of the control value (gto=0.0826 nS/pF) coinciding with the recommendation of [7] in atrial cells (Figure 1).



(A) (B)

Figure 1 Model of potential cellular action during stimulation at 1 Hz under physiological conditions (A) and electrical remodeling (B)

At the cellular level, the APD in controlling conditions has a duration of 305 ms and in remodeling conditions 137 ms showing a decrease of 55%, very close to the values reported by [10, 11] in 1D and 2D, which exclude the fiber orientation.

Anatomical model

A detailed and realistic geometrical model of human atrium was developed, starting from the clumsy model of [12]. The three-dimensional anatomical model obtained includes fiber orientation for both atria (left atrium (LA) and right atrium (RA)) in which the sinoatrial node (SAN), crest terminalis (CT), the fossa ovalis (FO) and its ring, the septum spurium, Bachmann's bundle (BB), twenty pectinate muscles (PM) in the RA free wall (Figure 2), the interatrial septum, left and right appendages (LAPG and RAPG), left and right pulmonary veins, superior and inferior vena cavas, the isthmus of RA, vestibule of the tricuspid valve, vestibule of the mitral valve and the coronary sinus can be highlighted. The surface adjusted to the natural atrial anatomy following histological observations and the details described in experimental studies [13, 14].

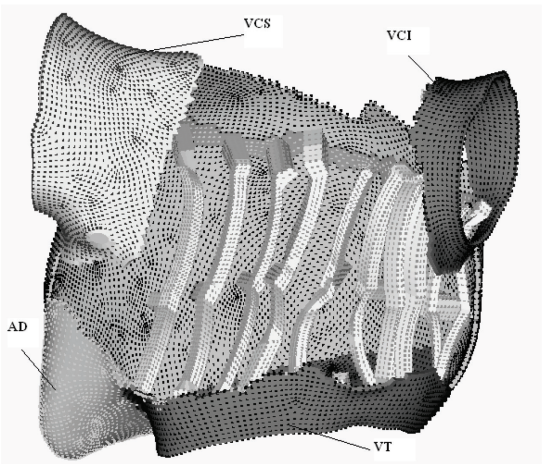


Figure 2 Assembly of pectinate muscles included in the model. VCS=Superior vena cava, VCI= Inferior vena cava, VT= Tricuspid valve orifice, AD= Right appendage

Fibers Orientation

The method we have used is based on previous studies [15]. Our model was divided into 42 areas according to the orientation of the main muscle bundles (circular, longitudinal, transverse or oblique) in order to separate tissue areas whose fiber direction is uniform. Once the region was defined, we determined the local vector direction of the fiber, considering the effect of the tissue curvature. To determine this, it was necessary to create an imaginary cylinder that wrapped that tissue, in which a case guideline was traced as the axis of the imaginary cylinder, a line in space sufficiently separated from the tissue as to wrap it up. The tangent lines of the cylinder correspond to the tissue fibers.

Conductivity Properties

In our model, three regions to establish high, medium and low conductivity were considered. The high conductivity regions corresponded to Bachmann's bundle, crest terminalis and pectinate muscles; the low conductivity regions corresponded to isthmus and SAN region. The other regions were taken as conductivity medium. The oval fossa region was considered non-conductive.

The tissue diffusion constants were set so that the conduction velocity was consistent with the experimental data [16, 17]. The diffusion tensor values obtained for both models were 0.6 for high conductivity, 0.2 for medium conductivity and 0.1 for low conductivity. For both models, anisotropy was set according to the relationship between longitudinal and transverse propagation velocity with 10: 1 at the crest terminalis [18] and 3:1 for the rest of atrial tissue. The longitudinal direction followed the path of the tissue fibers.

Numerical and computational methods

The monodomain model, which represents the electrical propagation of AP along a three-dimensional tissue is described by the following reaction-diffusion Eq. (1) [2, 19]:

$$\nabla \cdot (D_i \nabla V_m) = C_m \frac{dV_m}{dt} + I_{ion} \text{ in } \Omega \quad (1)$$

Where V_m represents the potential in the intracellular space, D_i is the anisotropic conductivity tensor, C_m is the membrane capacitance, and I_{ion} corresponds to the set of currents describing the ionic state of the cells in the tissue as a function of time and ionic concentrations. An extracellular space with infinite resistance is assumed.

With the following boundary conditions (Eq. 2):

$$(D_i \nabla V_m) \cdot n = 0 \quad \text{in } \Gamma\_n \quad (2)$$

where n is the normal vector to surface.

To solve the equation (1) of diffusion reaction, a parallel code using the finite element method (FEM) was implemented. A system of linear equations with nonlinear reactive term represented by I_{ion} appears from this discretization. The term reactive is explicitly solved while the temporal equation is solved implicitly.

A hexahedral mesh was built from the three-dimensional anatomical model that includes 52906 elements and 100554 nodes with a spatial resolution ranging from 300 to 700 μm. Eq. (1) was numerically solved using the software EMOS [20]. The time step was fixed at 0.0025 ms.

Stimulation protocol

The stimulation protocol implemented in this model is the standard S1-S2 protocol. Initially, a pulse train (S1) is applied in the region of the SAN node with a basic cycle length (BCL) of 600 ms, a duration of 6 ms and an amplitude of 60 uA in an area of approximately 10 mm2; subsequently, a premature stimulus S2 corresponding to an ectopic focus applied to a small group of cells of about 3 mm2 on the basis of the inferior vena cava is caused. The S2 stimulus was applied in the repolarization phase of the tenth sinus rhythm.

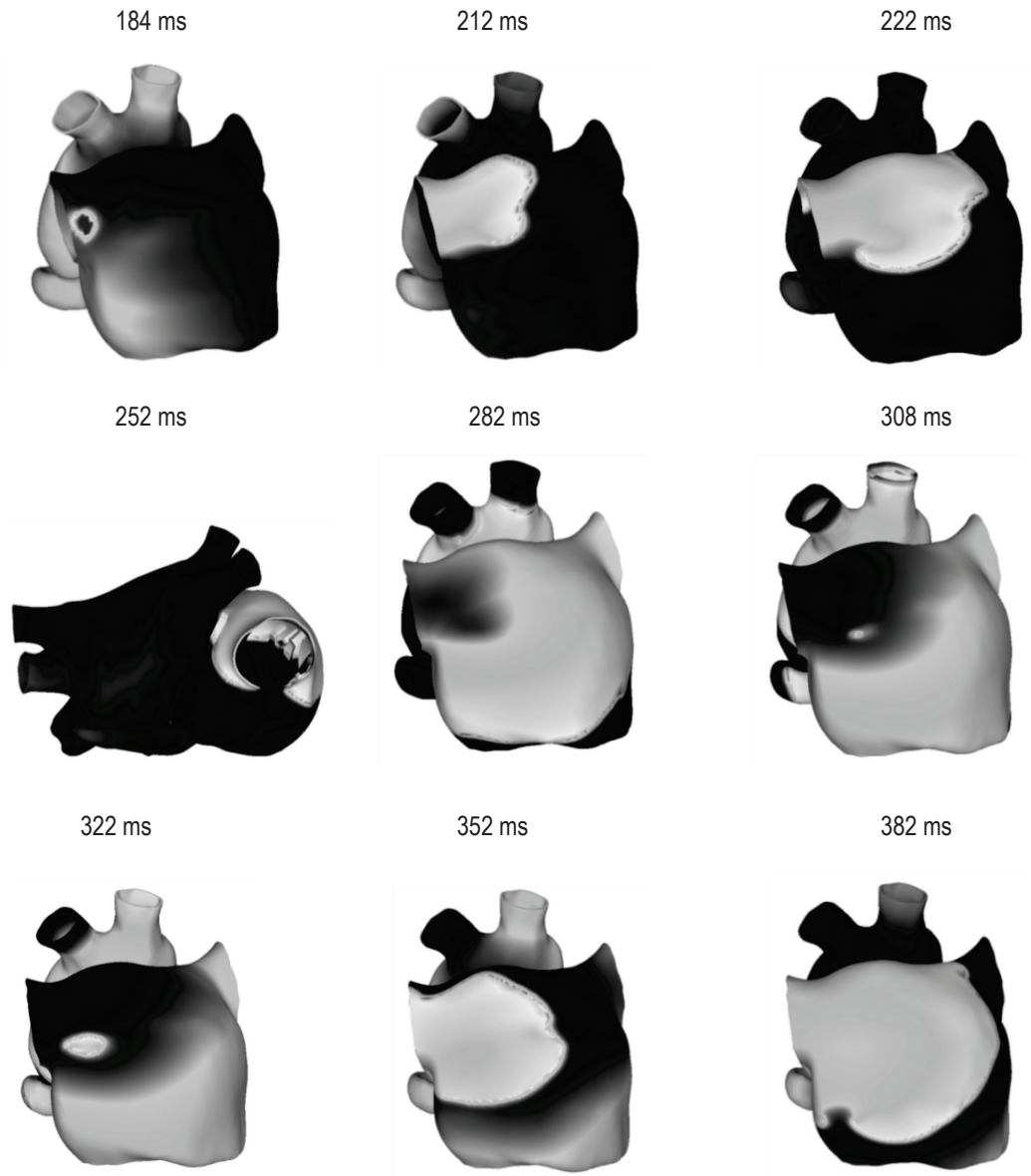
Results

When applying an ectopic focus at the base of the inferior vena cava, the protocol established was followed. Subsequently, the activation front spreads in the direction of the superior vena cava; the other end goes through the inferior vena cava to the atrioventricular region; the upper end is directed toward the intercaval beam in search of the superior vena cava facilitated by the displacement of the front in the direction of the tissue fibers and the high conductivity in the crest terminalis. The front propagates through the free wall of the right atrium forming a wave that stimulates the basis of the PM generating an anisotropic reentry that repeats in time.

Figure 3 shows the propagation sequence of the electrical impulse generated from a focal stimulus triggered in the inferior vena cava to the 182 ms of the coupling interval time for the electrical remodeled atrium model. At 212 ms, it can be seen how the front moves faster toward the superior vena cava due to the direction of the tissue fibers and the high conductivity of the crest terminalis. At 222 ms when the front takes the crest terminalis, it progresses faster reaching the base of the superior vena cava, while the slow front moves in the direction of the mitral valve around the inferior vena cava. This last front curves in the form of a spiral and reaches the PM located in the upper area of the right atrium at 228 ms. This wave front has a convex curvature that causes a reduction in the conduction velocity [21, 22]. In addition, it has been shown that changes greater than 1 mm in the thickness of tissue produce a "source-sink" imbalance [23] which along with other electrophysiological factors contributes to the front curvature. At 247 ms the front coming from the crest terminalis reaches the fossa ovalis transversally and propagates in the direction of the left septum. At 260 ms, the wave front completely surrounds the inferior vena cava and reaches a repolarization level of -84.45 mV in the source. The front covers the septum of the left atrial and is located at the base of the right pulmonary veins at 282 ms. At 318

ms the front that travels through PM in the lower part of the atrium reaches a free wall generating a new front and therefore, a reentry. The process is repeated indefinitely, exchanging different pectinate muscles.

This reentry generates a new activation front that again extends through the same area, thus creating a new reentry caused basically by the anisotropic properties and its non-uniform distribution in the three-dimensional tissue [24].



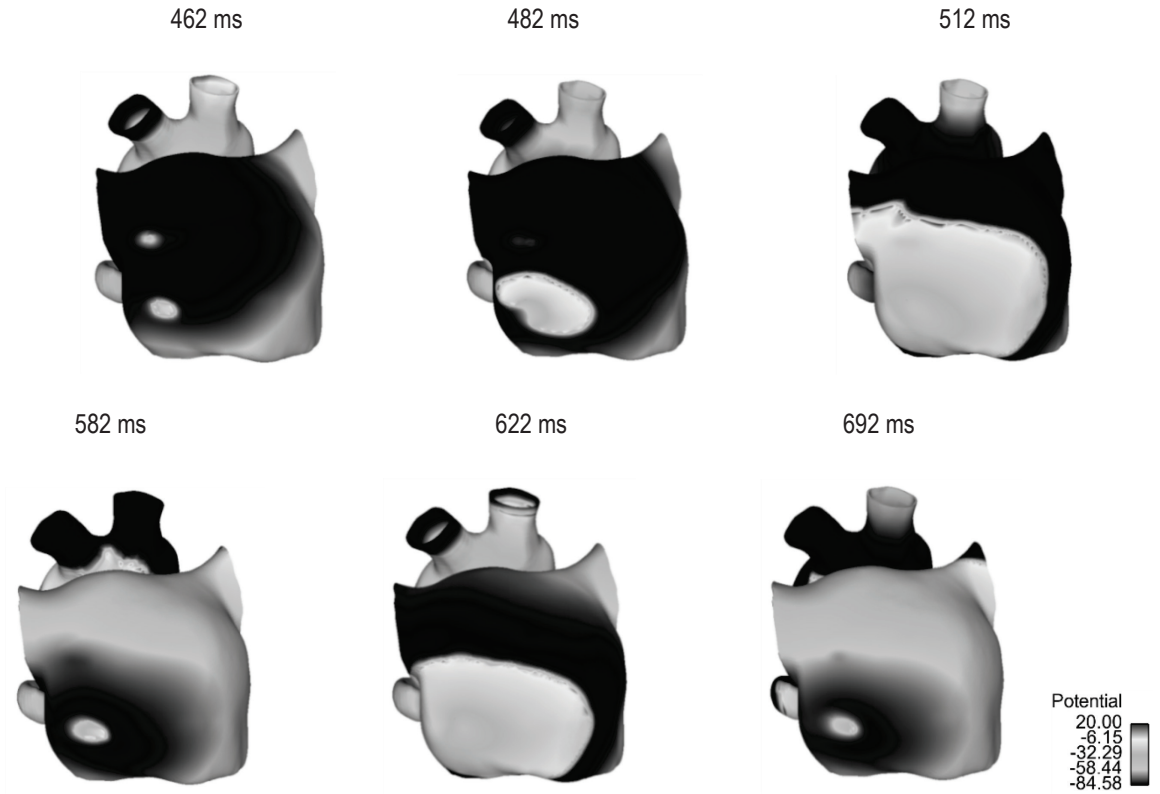
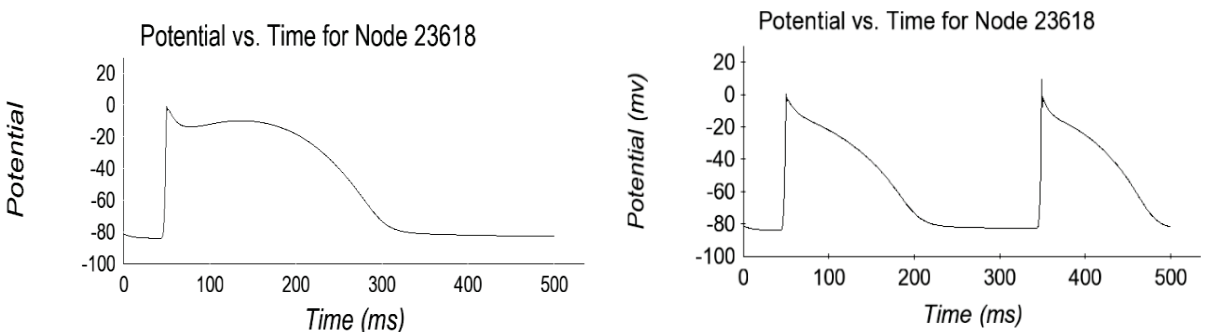


Figure 3 Ectopic focus at the base of the inferior vena cava in electrical remodelling conditions. (Potential in mV)

In the physiological model, the APD in tissue at 90% of repolarization (APD90) was of 235 ms and the model with electrical remodeling was of 144 ms, indicating a 39% decrease. The Effective refractory period (ERP) was reduced from 260 ms to 160 ms (Figure 4).



(A) (B)

Figure 4 AP obtained in the tissue model for node 23618 under physiological conditions (A) and electrical remodeling (B)

Discussion

Our results characterize the dynamics of the propagation of nonlinear waves in the anatomical structure of the PM in electrical remodeling situation finding that they constitute a structure that promotes the generation of reentry, due to the existence of preferential conduction pathways that are directly related to the crest terminalis, as was stated above [5]. Also, they provide a natural anchoring to the front of the reentrant wave. The area where a thickening of the atrial tissue is found forms a region prone to generate a breakdown of the wave front by facilitating the initiation and maintenance of reentries similar to those obtained in simulation studies [4].

On the other hand, our study shows that the appearance of ectopic activity at the base of the inferior vena cava can trigger atrial fibrillation; these results are consistent with previous experimental studies showing the case of an atrial tachycardia originating from within the inferior vena cava [25]. We have found a direct relationship between the ectopic activity at the base of the inferior vena cava and the generation of reentries in the PM. We do not have any notice of previous studies that have observed this relationship.

It was demonstrated that both the cellular dynamics and anatomy affect the initiation and maintenance of AF, situation which will require detailed understanding of potential ionic mechanisms that determine the dynamics of the rotors because, without doubt, this dynamics underlies the electrical activity in the most lethal arrhythmias [26, 27].

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