Modeling the Influence of High Fibroblast Level on Arrhythmia Development and Obstructed Depolarization Spread

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Abstract

Aims: In the focus of this study stand the fibroblast cells that under physiological terms are providing structural support for the heart, but under patho-physiological conditions they can obstruct the pacemaker activity and the excitation spread function of the heart that may develop arrhythmia.

Methods: We investigated the influence of high fibroblast level under several patho-physiological conditions. The simulation was performed on a 3D heart model, adopting a 0.25 mm spatial and 2 μs temporal maximal resolution. In our simulation 25% volume of the normal cardiac tissue is occupied by fibroblast, and in presence of pathological cases or aging, the fibroblast cells accumulate up to 40%-95% volume. We employed the effect of cardio-myocyte death and laminar sheets.

Results: In presence of 30%/35%/40%/45%/50% fibroblast in cardiac myocyte, the spread velocity of depolarization was obstructed by 3%/7%/11%/15%/19%, while regional inflammation and injures locally reduced the propagation speed of excitation by at least 20%. Tissue aging has reduced cardiac pacemaker activity and increased the possibility of irregular cardiac activity.

Conclusion: High fibroblast levels not only detains significantly the spread of excitation, but it can obstruct the depolarization wave evolving cardiac arrhythmia.

1. Introduction

The bulk of the cardiac cell population is formed by cardiac fibroblasts. They have a major impact on the structural, electrical and mechanical properties of the cardiac tissue. In spite of their high effect on cardiac functionality, these cells are frequently ignored [1].

Usually, cardiac myocytes are significantly larger then fibroblasts. In a healthy adult cardiac tissue, myocytes form about three fourths of the total volume, but they account only for one third of the total number of cells [2]. The bulk of the remaining 60-65% consists of fibroblasts, which besides maintaining the extra-cellular matrix network, have a critical contribution in cardiac tissue repairing after a myocardial infarction. These cells are populated everywhere in the cardiac tissue, and by surrounding the myocytes they form bridges between the myocardial tissue layers.

In the presence of diverse pathological cases, such as ischemic and rheumatic heart disease, inflammation, hypertrophy, and infarction, the rate of fibroblast is increased due to their maintained proliferative potential [3]. Beside the above mentioned reparation role after myocardial injuries, fibroblasts contribute to the development of the myocardial structure, and they influence the cardiac cell signaling and therefore the electrical and mechanical properties of the heart [4-6].

Injured or aged cardiac muscles, beside reduced reparative capabilities, are often linked with accentuated fibrosis and obstructed depolarization spread. Along the cumbered depolarization activity, the occurrence of diastolic dysfunction represents a severe danger, because it reduces locomotion functions and life quality of the patient.

In the last decades, several mathematical models and intelligent computational methods were developed in order to perform real-time computerized simulations of the whole heart, creating a useful tool to study cardiac dynamics [7, 8]. These simulations possess several advantages: they are not perturbed by data acquisition errors, the simulated values of all internal variables may be visualized, the size and nature of the healthy and injured cardiac tissue may be studied before the real intervention, and the simulation may be stopped at any moment for further improvements [9]. Despite the enrolled advantages, accomplishing a high-resolution spatial computerized simulation still remains difficult. The main performance limiting factor represents the erroneous initialization of the model's parameters and the high computational power demand.

Beside visual representation of medical data and parameters, cardiac models also facilitate the recognition

of several pathological events, such as various arrhythmias that may cause deadly ventricular fibrillation. This pathological event recognition process requires the inclusion of the fibroblast in the simulation; otherwise the obstructed depolarization and the forming mechanism of reentry circuits cannot be properly modeled [10]. The proper recognition of the arrhythmia's onset depends on details such as the heart's size [11], geometry [12], mechanical [13] and electrical state [14], anisotropic fiber structure [15], and inhomogeneity [16].

In the following we present the relation among injured cardiac tissue, accentuated fibrosis phenomena, obstructed depolarization and increased re-entry circuit development, in order to enhance the recognition and modeling of dangerous arrhythmias and perturbed cardiac pumping activity.

The rest of the paper is organized as follows: Section 2 gives a detailed description of the role of fibroblasts in the cardiac excitation and contraction for normal and pathological cases. Section 3 presents and discusses several aspects of the altered depolarization, and the results of simulations. In Section 4, the conclusions are formulated.

2. Methods

Most cardiac electric activity simulations are performed in two main manners. The first one involves several partial differential equations (PDE), where the local trans-membrane potential is determined by a mono-domain or bi-domain propagation model [17]. The second methodology stems from the application of cellular automata systems (CAS). These environments can handle several cardiac aspects, such as anisotropic tissue, modifiable geometry, and laminar sheet conduction, so they may properly model different physiological cases, such as left ventricular hypertrophy or extreme ventricular dilatation. Beside the possibility to model a vast group of pathological cases, CAS are appropriate to handle highly inhomogeneous cardiac tissue, such as local or extensive fibrosis, which is characteristic to cardiac injuries or infarct.

To perform the depolarization spread in highly inhomogeneous environment (HIE), we started from our older CAS-based heart model [9]. However, the HIE modeling cannot be performed without several important modifications.

As long as many important properties related to the compartment, such as type, state, size, activation potential function were maintained, several important aspects of the model were modified. First of all, a new Purkinje fiber system (PFS) was constructed in order to significantly reduce the spread propagation errors. This PFS works beside the old compartment-based model, and supplements the depolarization spread ways. Each compartment that has common part with PFS contains at least one reference point. The depolarization moment of the compartment C is given by the formula:

$$DT_C = \min_i \{d(C, RP_i) \cdot S_{DW_C} + DT_{RP_i}\},$$

where $d(A,B)$ represents the Euclidean distance between points A and B, RPi stands for reference point number i, while S_{DW_C} is propagation speed of the DW in the compartment C. The compartments situated close to the epicardium are not connected to the PFS, so their depolatrization time is given by the formula:

$$DT_C = \min_i \{d(C, C_i) \cdot S_{DW_C} + DT_{C_i}\},$$

where C_i represents the neighbors of the studied compartment.

The introduction of PFS changed the relation system among compartments. In the old model each compartment was connected only to its neighbors, so the inclusion of a PFS in the heart model could be done only by the implicit type change of the compartments. This approach makes difficult to change the shape or structure of the PFS, because all compartments have to be regenerated. Another simulation problem represented the compulsion to use relatively small compartments due to the complex multi-branched shape of the PFS. Beside these limits of the old model, due its diverse shape, the fibroblast system was totally ignored.

In our new model the fibroblast created cardiac matrix has three constituents: the epi-, peri- and endomysium. The epimysium (EPM) enfolds the endo- and epicardial surfaces. The perimysium (PEM) is linked with EPM and enshrouds each group of cardiac muscle fibers. The endomysium (EDM) is connected to PEM and enmeshes individual cardiomyocites. This matrix highly influences the cardiac pumping activity by transmitting contractile forces and electrically separating the atria and ventricles.

The incidence of fibroblast in the cardiac tissue strongly influences the propagation speed of the depolarization wave (DW). For example, at places of accentuated fibrosis, the DW cannot propagate at all, while a mild increment of fibroblasts due aging or injures significantly slows down the spread of DW. The complex network of fibroblasts cannot be modeled due to resolution restrictions (an ordinary compartment contains about 10^3-10^6 cardiac cells), so their effect must be involved in the compartment's properties. A simplification formula involving the effect of extra-cellular gap junctions and fibroblasts was described by Rohr [18]. When the DW propagation is not totally obscured (at most 95% of the cells in the compartment are fibroblasts), we decreased the conduction speed of the ventricles from 36.7 cm/s (up to 60% fibroblast) to 0.3 cm/s (up to 95% fibroblast). This drastic decrement of DW in presence of serious fibrosis is caused by the often

occurred junctional uncoupling among cardiac myocytes and the meandering path of the DW, due the presence of several islands of completely uncoupled cells. These islands inhibit the connection among conducting cells, so they enforce the DW to follow a 'zig-zag' path.

The heart modeling was performed using various cellular models. The cellular activity of the sino-atrial node was simulated by the equations of Noble and Noble [19], while the atrial cell modeling is based on the work of Nygren et al. [20]. Inada et al. introduced an atrio-ventricular node model that involves atrio-nodal, nodal, and nodal-his cells [21]. We included their model in our simulation in order to handle the whole depolarization retentive sub-system of the heart. The electric activity of the ventricular cells was modeled by the Luo-Rudy II model [22-23], using a membrane capacity of 1μF/cm^2, and a temperature of 37°C. The Purkinje cells were modeled using the equations of McAllister et al. [24].

The simulation was performed on a 3D heart model, where the spatio-temporal resolution was 0.25 mm and 2 μs at the moment of depolarization, while in the other phases of the depolarization-repolarization cycle we used 0.5-2.5 mm and 20-500 μs resolutions [25, 26]. As mentioned above, totally five types of conducting cells were included in modeling of the DW propagation. The volumetric incidence of fibroblasts was 25% in the completely healthy tissue, while in the injured or inflamed regions fibroblast cells accumulate up to 40%-80% volume. Aging also increased the relative volume of fibroblasts from 25% to 30-50% for ventricular cells and up to 40-60% among sino-atrial cells. In regions plagued by serious infarction the fibrosis phenomena caused a 90-100% incidence of fibroblasts.

We assumed that the death-rate among normal cardio-myocytes was less than 15% (referred to the total number of conducting cells), and the laminar sheet isolation factor (the rate of depolarization velocity in in-sheet orientation to trans-sheet direction) is between 2-9. We considered that an increased fibroblast level not only disturbs the spread of the DW, but can develop ectopic beats with increased occurrence. In our consideration, a 60% fibroblast incidence increases the occurrence of spontaneous ectopic-firing (SEF) by 25 times (compared to normal circumstances), while a 90% incidence causes a 200 times more prevalent SEF.

3. Results and discussion

In Figure 1, the decreased excitation is presented in function of the volumetric rate of the fibroblasts. It can be observed that the apex region is somehow less sensible to the fibroblasts than the right posterior lateral region.

Figure 2 presents the slow-down of the ventricular depolarization process. As indicated in graph, the aging ventricular tissue is not only thicker, but contains much more fibroblasts, so it conducts the depolarization wave less efficiently. The normal conducting path of the excitation is longer from the septum to the right posterior lateral and left lateral locations than to the apex, so in a senescent heart these regions are excited much later.

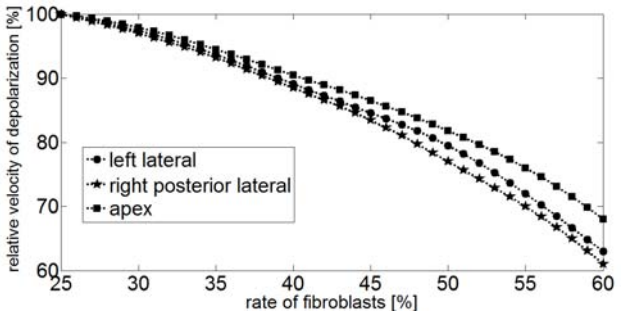

Figure 1. The relative velocity of depolarization in function of rate of fibroblasts.

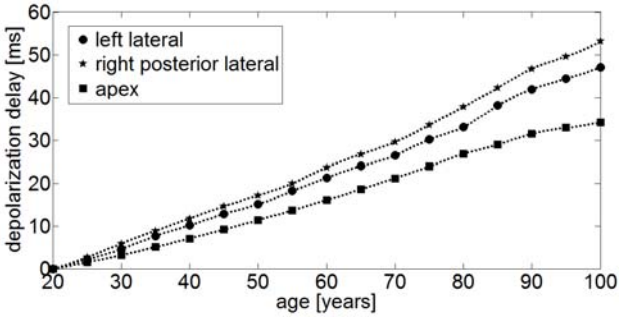

Figure 2. The deceleration of excitation in the ventricles in function of age.

The high fibroblast level favors an uneven propagation of the depolarization wave that can develop repeatedly re-exciting phenomena in the cardiac tissue. It is know that the bulk of arrhythmias are caused by reentrant excitation of the cardiac tissue, because the re-circulating depolarization wave excites the cells at a significantly higher frequency than the natural pacemaker SA-node.

From the simulation results and anatomical deductions we concluded that the development of the dangerous re-entry exciting waves is favored by: slow repolarization of the cardiac cells, long possible-exciting window, high excitation frequency, low excitation conduction speed, spacious heart size, thick ventricular wall, highly inhomogeneous cardiac tissue, increased self-ectopic firing occurrence, large non-conducting structures (such as main arterial).

4. Conclusion

The computerized simulation of fibroblasts provides a better appreciation of cardiac excitation, which may help to uncover the formation steps of arrhythmia. This non-

invasive tool may elucidate the development of dangerous arrhythmias. Besides giving a geometric representation of the cardiac tissue, a proper heart model can describe its functionality. This way it will become possible to determine several physiological parameters that are close to experimental results. An adequate simulation platform may be used to select the most endangered patients by a non-invasive method, thus contributing to the efficiency of computerized health care.

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