Pis'ma v ZhETF, vol. 119, iss. 9, pp. 712 – 713 May 10

Discrete anisotropy model of heterogeneous cardiac tissue predicting the occurrence of symmetry breaking of reentrant activity

S. A. Romanova[+*], A. K. Berezhnoy[+*×], L. E. Ruppel[+], A. A. Aitova[+*], S. S. Bakumenko[+×], I. S. Semidetnov[+], V. D. Naumov[+], M. M. Slotvitsky[+*×], V. A. Tsvelaya[+*×1)], K. I. Agladze[+*1)]

[+]*Laboratory of Experimental and Cellular Medicine, Moscow Institute of Physics and Technology, 141701 Dolgoprudny, Russia*

[*]*M. F. Vladimirsky Moscow Regional Research Clinical Institute, 129110 Moscow, Russia*

[×]*ITMO University, 197101 St. Petersburg, Russia*

Submitted 20 March 2024
Resubmitted 20 March 2024
Accepted 4 April 2024

DOI: 10.31857/S123456782409012X, EDN: ALSOWB

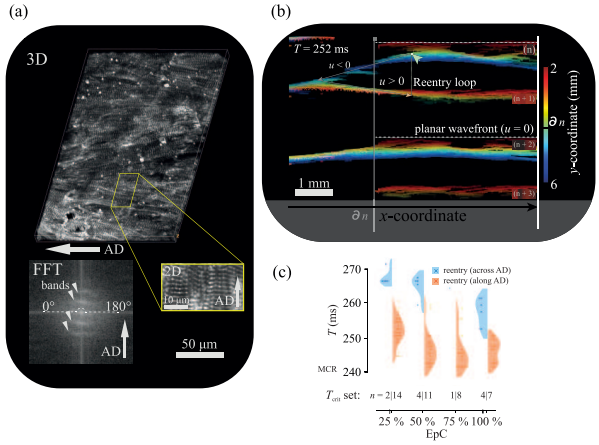

Fig. 1. (Color online) (a) – Confocal micrographs of a section of anisotropic tissue, Fast Fourier transformation of the pattern of transverse banding of the actinin cytoskeleton. AD is shown as white arrow. (b) – Spatio-temporal graphs of the movement of the leading wave front during the formation of reentry in a high-frequency wave train. Here, the spatial x-coordinate is plotted along the horizontal axis, the y-coordinate is displayed through color-coding, and time is plotted along the vertical axis (from top to bottom), u denotes the projection of the CV onto the x-axis. Semi-translucent white arrows and a vertical dotted line show the closure of the reentry loop for wave (n). The $(n+1)$ wave annihilates with the resulting spiral wave. (c) – Dotted and violin plots showing the distribution of T_{crit} at different values of EpC and different orientation of AD in the samples

Cardiac arrhythmias are a major cause of cardiovascular mortality worldwide. Coordinated and efficient functioning of cardiac tissue is possible due to the sequential transmission of electrical excitation between cardiomyocytes, the working cells of the heart. This transfer of excitation is carried out by intercellular connections of different biological nature – their variability presumably determines the anisotropy of the conduction velocity (CV) of the excitation waves [1]. Cardiac tissue displays significant heterogeneity in excitation conduction, with functional blocks and reentrant arrhythmia sources emerging from the inhomogeneities in conduction, challenging the assumptions held by conventional homogeneous models [2]. Our aim in this study was to create a computational model of cardiac tissue that will allow us to take into account the role of intercellular connections in the desynchronization of cardiac excitation.

For this purpose, two models of cardiac tissue were involved in the study – a two-component computational model (*in silico model*) and an experimental model based on a cellular culture of neonatal rat cardiomyocytes (*in vitro model*). The computational model consisted of the Cellular Potts Model (CPM), used for the biologically correct distribution of intercellular contacts [3] and the electrophysiological Courtemanche model, which describes the generation and propagation of electrical excitation [4]. Two types of intercellular conduction were introduced in the computational model: gap junctional and ephaptic intercellular coupling. Both in *in vitro* and *in silico* model, the anisotropy direction (AD) was specified in the samples, i.e. orientation of fibers in cardiac tissue. In both cases, samples of the same size (up to 15 mm) were created with a non-conducting geometric obstacle having a non-flux boundary. To visualize the excitation wave train in the experimental samples, the fast calcium-dependent fluorescent label Fluo4-AM was used.

We investigated the conditions under which reentrant spiral waves can be generated by a high-frequency planar wavetrain in the vicinity of a rectangular geo-

[1)]e-mail: valeriyatsvelaya@gmail.com; agladze@yahoo.com

metrical obstacle. The key idea is that the combination of a rectangular non-conducting obstacle with a global anisotropy direction aligned with one of its sides makes it possible to maintain the symmetry of the obstacle's tip both when AD or anisotropy ratio (AR) are changed (where AR is the ratio of CV along AD and across). We formalized the influence on tissue arrhythmogenicity through a relative change in the vulnerable frequency corridor: a set of values of the stimulation period T_{crit} at which reentry formation is possible.

We defined that the set of T_{crit} shifts and expands when AD is rotated, while the spiral wave circulation period and the maximum captured rate (MCR) remain unchanged. The experimental model showed qualitative consistency with computational results in terms of T_{crit} distribution. At the same time, both models refute the assessment of changes in T_{crit} made using eikonal equation with homogeneous approximation, which indicates the limit of applicability of the homogeneous models when describing the occurrence of primary reentry. Figure 1a shows the alignment of actinin cytoskeleton structures in a monolayer of rat cardiomyocytes; a similar organization of intracellular structures was achieved in our computational model. Figure 1b shows a spatiotemporal sweep depicting the propagation of the leading edge of the excitation wave during the formation of reentry. Figure 1c shows the model-predicted shift in T_{crit} values, which was confirmed in a tissue culture experiment.

We have further studied the dependence of arrhythmogenicity on the mechanism of cellular coupling: we found that ephaptic type of conductance (EpC) directly controls the spread of T_{crit}. These results could be useful for explanation of cases where non-selective modulation of ion channels can synergize with changes in EpC.

As a result, we derived a theoretical formulation of CV anisotropy and validated it through *in vitro* and *in silico* functional experiments as an effective tool for predicting primal reentry. Joint theoretical and experimental analysis of the relationship between the cardiac tissue structure and its function revealed two aspects. The first one consisted in limitation of the applicability of the homogeneous formulation of conduction anisotropy when studying primary reentry, since the nature of intercellular heterogeneities plays a crucial role in the sustainable growth of a unidirectional block. The second one showed up in the distinct role of gap junctional and ephaptic coupling in stabilizing the high-frequency wavetrain, which modulates tissue arrhythmogenicity bypassing the well-known factors such as modulation of ionic currents.

Funding. The work was supported by the Russian Science Foundation (Research Grant # 23-74-01028).

Conflicts of interest. The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Ethics approval and consent to participate. All the experimental studies conformed to the Guide for the Care and Use of Laboratory Animals published by the United States National Institutes of Health (Publication # 85-23, revised 1996) and approved by the Moscow Institute of Physics and Technology Life Science Center Provisional Animal Care and Research Procedures Committee, Protocol # A2-2012-09-02.

This is an excerpt of the article "Discrete anisotropy model of heterogeneous cardiac tissue predicting the occurrence of symmetry breaking of reentrant activity". Full text of the paper is published in JETP Letters journal. DOI: 10.1134/S0021364024600782

1. A. G. Kléber and R. Yoram, Physiol. Rev. **84**(2), 431 (2004).
2. D. N. Hajian, F. Parastesh, S. Jafari, M. Perc, and E. Klemencic, Chaos, Solitons & Fractals **179**, 114413 (2024).
3. G. Francois and J. A. Glazier, Phys. Rev. Lett. **69**(13), 2013 (1992).
4. M. Courtemanche, R. J. Ramirez, and S. Nattel, Am. J. Physiol. Heart Circ. Physiol. **275**(1), H301 (1998).
5. N. Kudryashova, A. Nizamieva, V. Tsvelaya, A. V. Panfilov, and K. I. Agladze, PLOS Comput. Biol. **15**(3), e1006597 (2019).
6. V. N. Kachalov, V. A. Tsvelaya, N. N. Kudryashova, and K. I. Agladze, JETP Lett. **106**, 608 (2017).