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Investigating Calcium-Mediated Arrhythmias via a Computational Model of a Rabbit Atrial Myocyte

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Abstract

The system of transverse and longitudinal sarcolemmal tubules (T-system) is observed to remodel in atrial fibrillation (AF) and heart failure (HF). The resulting calcium dysregulation has been suggested to underlie disruptions in excitation-contraction coupling, and increase the frequency of arrhythmic events at the cellular scale; however, these mechanisms and their importance are yet to be fully described. A stochastic, 3D, spatio-temporal model of the rabbit atrial myocyte was developed in order to study calcium-mediated arrhythmic phenomena at the cellular scale. Preliminary findings suggest a relationship between the severity of detubulation, and the promotion of spontaneous activity, and provides insight into the conditions required for the emergence of spontaneous activity within atrial myocytes in HF.

1. Introduction

The morphology of the system of transverse tubules (T-system) in atrial myocytes is conjectured to be remodeled within atrial fibrillation (AF) and heart failure (HF) [1], two cardiac conditions of increasing prevalence [2], with one condition often leading to the development of the other [2, 3]. Patho-physiological aberrations in calcium (Ca^{2+}) handling systems, considered to involve alterations in T-system structure and remodeled channel expression, are suggested to promote both disrupted excitation-contraction coupling and an increasing frequency of arrhythmic events at the cellular scale [4]; the importance of T-system remodeling in the development of pro-arrhythmic events such as spontaneous Ca^{2+} release remains unclear [1].

We aimed to develop a multi-scale, rabbit-specific atrial myocyte model, incorporating the relevant stochastic spatial-temporal Ca^{2+} handling dynamics in 3D, required to produce a platform capable of studying Ca^{2+}-mediated arrhythmia mechanisms.

2. Methods

A contemporary model describing rabbit atrial electrophysiology produced by Aslanidi *et al.* [5, 6] (Figure 1A), was integrated with our model describing stochastic, spatio-temporal Ca^{2+} dynamics [7, 8] (Figure 1B). Atrial T-system remodeling, associated with HF, was incorporated in isolation from other forms of remodeling which may occur, through the removal of sarcolemmal ion channel currents from individual Ca^{2+}-release units (CRUs, Figure 1B) randomly, varying both total percentage detubulation of the cell, and the patch size of detubulated regions (Figure 1C).

Rapid pacing protocols were applied to load the sarcoplasmic reticulum (SR) Ca^{2+} content, to promote the propagation of spontaneous Ca^{2+} waves; a general implementation of a pro-Ca^{2+} overload condition was also considered, representing remodeling and/or an intervention such as isoprenaline, in which I_{CaL} and SERCA activity is enhanced. All simulations presented in this study took place in cells with a CRU network of 15 × 20 × 65 CRUs along the X, Y and Z axes respectively.

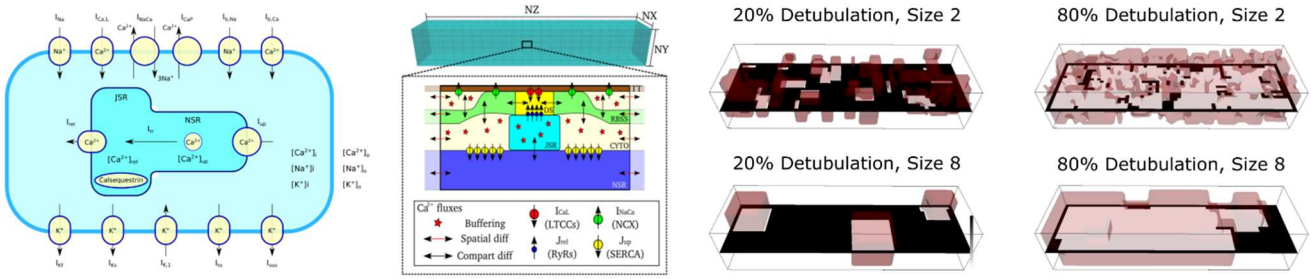

Figure 1 - Structure of the atrial myocyte models used. Membrane current formulations from the Aslanidi *et al.* [5] model of a rabbit left atrial myocyte (A) were incorporated into the Colman *et al.* [7] stochastic Ca^{2+} framework (B). Patches of detubuluation (C) were introduced through the removal of sarcolemmal ion channels, at various sizes to detubulate some percentage of the cell to represent T-system remodeling.

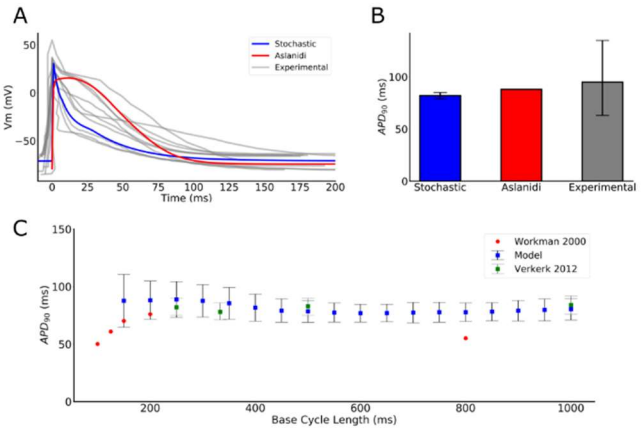

Figure 3 - Action potential (AP) dynamics. A) Rabbit left atrial APs of the newly developed (blue) and Aslanidi *et al.* (red) models (Figure 1), along with a range of experimental APs on rabbit left atrial myocytes. B) The AP duration (APD) of the Stochastic, Aslanidi *et al*. and experimental APs shown in A. C) The AP restitution curves from Workman *et al*. [10] and Verkerk *et al.* [9]

3. Results

3.1. Action potential dynamics

The stochastic model developed produces an action potential within the ranges of experimental data (Figure 2A), and has morphological differences to the original model, such as a visible spike in the rapid upstroke and a triangular morphology, primarily determined by a significantly different cytosolic Ca^{2+} transient (CaT) morphology, the sodium-calcium exchanger, and I_{CaL} Ca^{2+}-induced inactivation. Both the stochastic and Aslanidi *et al.* models fall well within the range of experimental APDs (Figure 2B) at a base cycle length of 500 ms. The AP restitution curve indicates that the stochastic model produces APDs which agree with the AP restitution studies by Verkerk *et al*. [9] and Workman *et al.* [10] (Figure 2C).

3.2. Effects of detubulation on stimulated Ca^{2+}-wave propagation.

The degradation of the T-system was shown to produce a CaT with a progressively slower upstroke as the density of the T-system was reduced (Figure 3A). The peak of the CaT decreases slightly due to the lower number of L-type Ca^{2+} channels present within the cell, but was not significantly smaller in the fully detubulated cell compared to control. The slower upstroke was a result of fewer CRUs activating instantly (corresponding to those not coupled to a cluster of LTCCs) and thus being activated by slower propagation of Ca^{2+} from the T-system positive regions (Figure 3B).

Propagation of Ca^{2+} throughout the Y-Z plane of the cell is shown in each of the three cases of detubulation (Figure 3C). The control cell shows familiar, near-simultaneous fast rise of intracellular Ca^{2+}, followed by uniform decay. The fully detubulated cell displayed rapid rise along the cell surface, which diffuses through the cell, exciting neighboring CRUs through a diffusion-recruitment process which is significantly slower than a cell with a full T-system. The partially detubulated cell displays a combination of both behaviors, with unaffected regions undergoing the rapid, near-simultaneous increase in Ca^{2+} throughout the cell, followed by the Ca^{2+}-wave propagating slowly into the detubulated regions.

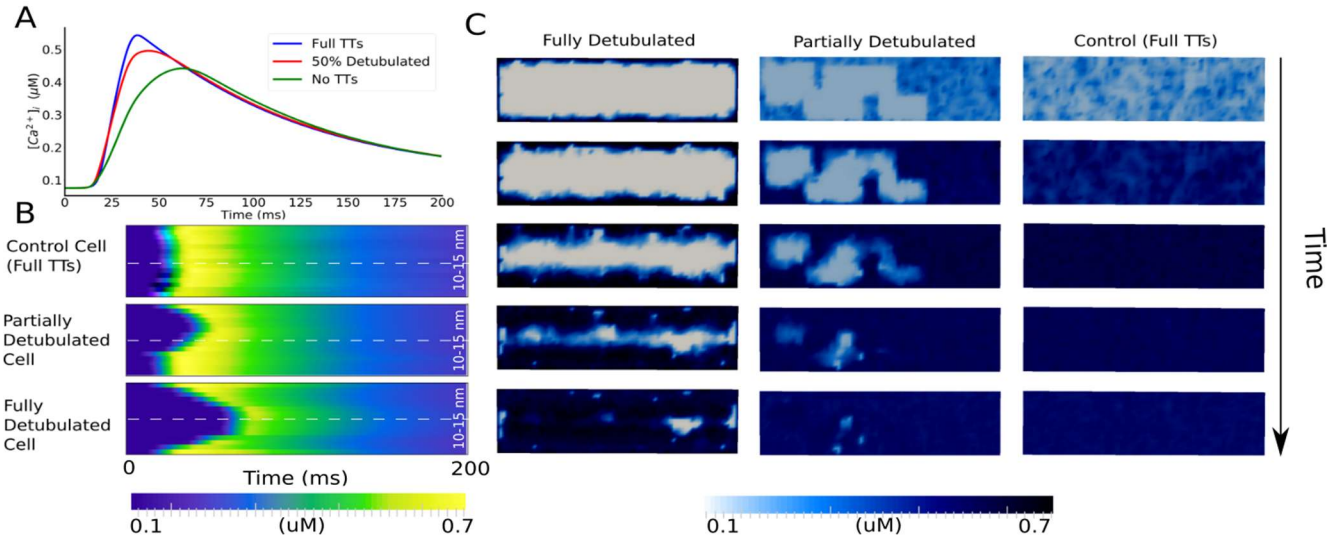

Figure 2 - Effects of detubulation on stimulated Ca^{2+} wave propagation. A) Intracellular Ca^{2+} transient for a fully, partially and none-detubulated cell in the stochastic model. B) Linescans along the X-axis of the cell over 200 ms. C) Intracellular Ca^{2+} snapshots along the Y-Z plane of fully, partially and none-detubulated versions of the stochastic rabbit atrial myocyte cell model.

3.3. Detubulation promotes spontaneous activity under SR Ca^{2+} loading

A total of nine simulations under each set of conditions were performed, the results of which show few, uncommon spontaneous activity among detubulated cells without the presence of a pro- Ca^{2+} loading condition, but all simulations show significant magnitudes of spontaneous excitation with the presence of such a condition.

The results (Figure 4) show a positive correlation between total percentage of detubulation and the average magnitude of changes in $[Ca^{2+}]_{NSR}$ for spontaneous activity across the nine simulations, for 20%, 40% and 60% detubulation. This suggests that atrial remodeling in the form of modifications to T-system morphology may promote spontaneous activity, however this relationship is not linear.

A negligible difference on the average relative magnitude of spontaneous activity across the patch sizes at each severity of T-system remodeling also suggests that the patch size of these detubulated regions may be unimportant for the magnitude of spontaneous Ca^{2+} activity. However, there was a correlation between the location of the boundaries of detubulated regions and the origin of spontaneous Ca^{2+}-waves.

4. Discussion

The implementation of a stochastic, 3D, spatio-temporal Ca^{2+} handling framework to the Aslanidi *et al.* rabbit atrial myocyte model (Figure 1) has produced a more physiological CaT morphology while retaining a physiological AP (Figure 2A, 2B), and agreement with a range of experimental AP restitution curves (Figure C).

Ca^{2+}-wave propagation for a stimulated excitation (Figure 3) produces familiar behaviors for the control cell, and a slower propagation of Ca^{2+} through a diffusion-recruitment CRU mechanism, with the partially detubulated cell displaying a combination of these behaviors. Increasing the severity of the T-system remodeling, via increasing the percentage of the cell which was modelled to be detubulated, had a positive correlation with the average magnitude of spontaneous activity over the set of simulations produced (Figure 4). The results suggest that the removal of sarcolemmal ion channels as a result of T-system remodeling promotes spontaneous activity, in agreement with the findings of Song *et al*. [1] while the size of the remodeled regions have no significant effect on the average magnitude of these spontaneous events.

Initial analysis indicates that reduced Ca^{2+} efflux within the detubulated regions promotes spark-induced-spark propagation, and thus the development of whole-cell release events from Ca^{2+} sparks. Increased influx at the boundary of a detubulated region (compared to within the detubulated region) produces conditions which promote SR-Ca^{2+} increase, and thus may localize the origin of these release events to these boundary regions.

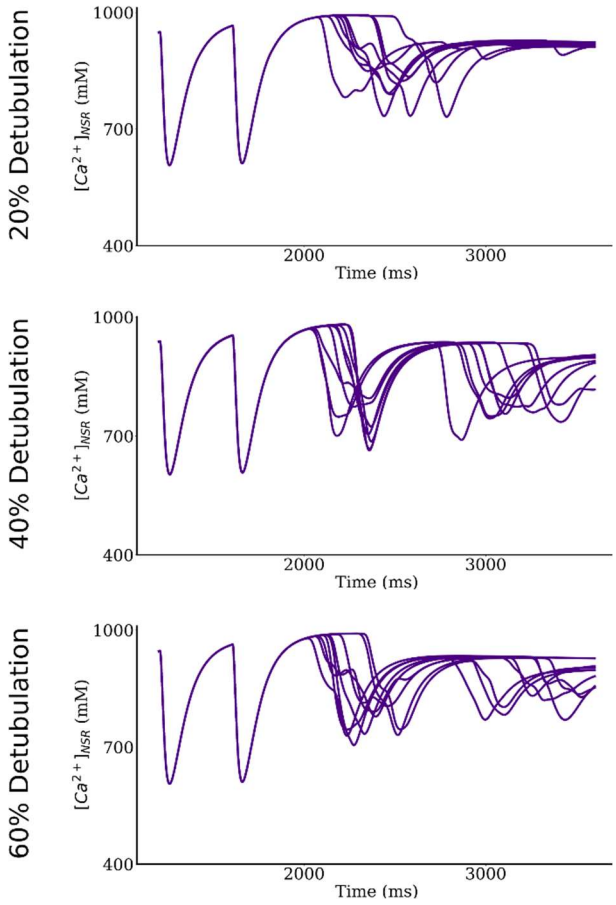

Figure 4 - Effects of detubulation on promoting spontaneous activity. A range of detubulation severities (percentage of total detubulation) and sizes (see Methods) underwent a general implementation of a Pro-Ca^{2+} loading condition, such as isoprenaline, in which I_{CaL} and SERCA activity is enhanced. Three plots of the same patch size are shown. As rabbits are known to have lower t-tubule densities, 20% detubulation can be considered as a control.

The emergence of spontaneous APs in the atria has been associated with arrhythmogenic triggers for AF. Our study provides insights into the conditions for the emergence of such triggers, as well as cellular models that can be integrated into 3D atrial models to simulate such triggers. Currently, even highly detailed 3D atrial models [11, 12] rely on fast pacing for the initiating of AF, and the introduction of a natural triggering mechanism will prove valuable in furthering the understanding of the complex mechanisms underlying AF.

5. Conclusion

A computational model of a rabbit left atrial myocyte has been produced from the Aslanidi *et al.* rabbit atrial model, and our model of stochastic, 3D, spatio-temporal Ca^{2+} handling. The model produces a physiological AP morphology, and reproduces APD dynamics observed in experimental studies. A representation of T-system remodeling was implemented, along with a general pro-Ca^{2+} loading condition. The model is capable of producing spontaneous Ca^{2+}-waves, and investigation into the relationship between T-system remodeling and spontaneous activity reveals several distinct behaviors of spontaneous Ca^{2+}-wave propagation, and a correlation between increased detubulation and the magnitude of spontaneous activity.

Acknowledgements

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References

[1] Song Z, Liu MB, Qu Z. Transverse tubular network structures in the genesis of intracellular calcium alternans and triggered activity in cardiac cells. *J Mol Cell Cardiol* 2018; 114: 288–299.

[2] Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014; 213.

[3] Heijman J, Voigt N, Nattel S, et al. Cellular and Molecular Electrophysiology of Atrial Fibrillation Initiation, Maintenance, and Progression. *Circ Res* 2014; 114: 1483–1499.

[4] Li Q, O'Neill SC, Tao T, et al. Mechanisms by which cytoplasmic calcium wave propagation and alternans are generated in cardiac atrial myocytes lacking T-tubules-insights from a simulation study. *Biophys J* 2012; 102: 1471–1482.

[5] Aslanidi OV, Boyett MR, Dobrzynski H, et al. Mechanisms of Transition from Normal to Reentrant Electrical Activity in a Model of Rabbit Atrial Tissue: Interaction of Tissue Heterogeneity and Anisotropy. *Biophys J* 2009; 96: 798–817.

[6] Aslanidi OV, Robinson R, Cheverton D, et al. Electrophysiological substrate for a dominant reentrant source during atrial fibrillation. *Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf* 2009; 2009: 2819–2822.

[7] Colman MA, Perez Alday EA, Holden AV, et al. Trigger vs. Substrate: Multi-Dimensional Modulation of QT-Prolongation Associated Arrhythmic Dynamics by a hERG Channel Activator. *Front Physiol*; 8. Epub ahead of print 4 October 2017. DOI: 10.3389/fphys.2017.00757.

[8] Colman MA, Pinali C, Trafford AW, et al. A computational model of spatio-temporal cardiac intracellular calcium handling with realistic structure and spatial flux distribution from sarcoplasmic reticulum and t-tubule reconstructions. *PLOS Comput Biol* 2017; 13: e1005714.

[9] Verkerk AO, Geuzebroek GSC, Veldkamp MW, et al. Effects of acetylcholine and noradrenalin on action potentials of isolated rabbit sinoatrial and atrial myocytes. *Front Physiol* 2012; 3: 174.

[10] Workman AJ, Kane KA, Rankin AC. Rate-dependency of action potential duration and refractoriness in isolated myocytes from the rabbit AV node and atrium. *J Mol Cell Cardiol* 2000; 32: 1525–1537.

[11] Aslanidi OV, Colman MA, Varela M, et al. Heterogeneous and anisotropic integrative model of pulmonary veins: computational study of arrhythmogenic substrate for atrial fibrillation. *Interface Focus*; 3. Epub ahead of print 6 April 2013. DOI: 10.1098/rsfs.2012.0069.

[12] Varela M, Colman MA, Hancox JC, et al. Atrial Heterogeneity Generates Re-entrant Substrate during Atrial Fibrillation and Anti-arrhythmic Drug Action: Mechanistic Insights from Canine Atrial Models. *PLOS Comput Biol* 2016; 12: e1005245.

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