ELUCIDATING THE ROLE OF THE HIS-PURKINJE SYSTEM DURING LONG QT MEDIATED ARRHYTHMIAS

Anthony Owusu-Mensah

Department of Electrical and Computer Engineering
Old Dominion University, Norfolk, USA
aowus003@odu.edu

Omer Berenfeld

Center for Arrhythmia Research Internal Medicine, Biomedical Engineering and Applied Physics
University of Michigan, Ann Arbor, USA
oberen@med.umich.edu

Michel Audette

Department of Electrical and Computer Engineering
Old Dominion University, Norfolk, USA
maudette@odu.edu

ABSTRACT

Long QT type 2 (LQT2) is a cardiac disorder caused by mutations in the hERG gene, which can lead to life-threatening arrhythmias. However, the exact involvement of the His-Purkinje System (HPS) in LQT2-mediated arrhythmias remains elusive. We utilized a computational model of the rabbit ventricles integrated with HPS to investigate the role of HPS in LQT2-mediated arrhythmia. We induced persistent reentry from an ectopic stimulus and isolated the HPS at different time points following the induction of reentry to determine its involvement in reentry dynamics. The earliest termination time for reentry coincided with the earliest time the HPS was isolated, indicating direct involvement of HPS in LQT2-mediated ventricular arrhythmia. Additionally, altering the HPS junctional parameters, such as coupling resistance or the number of myocytes at the Purkinje-Myocardial Junctions, affected reentry dynamics. Our multi-scale computer modeling outcomes offer important new understandings of probable arrhythmia mechanisms under LQT2 circumstances.

Keywords: Long QT Syndrome, hERG, His-Purkinje System, Purkinje-Myocardial Junction, Ventricular arrhythmia.

1 INTRODUCTION

Sudden cardiac death (SCD) from cardiac arrest occurs in approximately 300,000 persons annually in the United States, out of which 5% of the deaths occur in patients with morphologically intact hearts (Meyer et al. 2003). SCDs resulting from patients with structurally normal hearts is called sudden arrhythmia death syndrome (SADS) (Asatryan et al. 2021; Meyer et al. 2003) ,and the prevalence tends to be higher in younger subjects(Asatryan et al. 2021). Long QT syndrome (LQTS) (Moss, 2003; Priori et al. 2001; Roden, 2008) is among the clinical entities associated with SADS(Asatryan et al. 2021). LQTS is an electrophysiological disorder that is congenital or acquired through the intake of certain drugs, which potentiates the risk of developing ventricular tachyarrhythmias. LQTS is a substantial medical challenge in

terms of morbidity, mortality, and financial burden to the health care system. Initially considered a very rare condition, it is now estimated that LQTS is present in considerable proportions (1:3000 to 1:5000) in the general population (Zareba and Cygankiewicz 2008). A total of 15 gene mutations have been associated with autosomal dominant forms of congenital LQTS (Nakano and Shimizu 2016) but the most common conditions are LQT1, LQT2, and LQT3. LQT2 results from mutations in the hERG which impairs the rapid delayed rectifier potassium current (I_{Kr}) - a major outward current responsible repolarization in cardiomyocytes and a standard screen for drug safety (Fedida and Macdonald 2016), since most antiarrhythmic drugs block the current.

The His-Purkinje system (HPS) comprises of specialized cells responsible for the synchronous activation of the ventricles. The arborized architecture of the HPS is electrically isolated from the ventricles except at the Purkinje-myocardial junctions (PMJs) (Haissaguerre et al. 2016). The HPS cells are susceptible to the formation of abnormal depolarizations during action potential(AP) called early afterdepolarizations (EADs) (Schafferhofer-Steltzer et al. 2005) due to their high diastolic resistance (Huelsing et al. 1998). Therefore, the HPS may spread ectopic activity through the PMJs to the neighboring ventricular myocytes (VMs) (Li et al. 1992) to initiate ventricular arrhythmias. Purkinje cells surrounding ventricular myocytes in the subendocardium cannot be resolved by optical mapping, commonly used to study the anatomic origin of ventricular arrhythmias (Blackwell et al. 2022). Thus, although arrhythmia occurrence in LQT2 has been well documented, the exact involvement of HPS in LQT2 mediated ventricular arrhythmias has not been elucidated.

In this study we utilized a computer-based 3D anatomical model of rabbit ventricles integrated with a HPS to elucidate the role of HPS during LQT2 mediated ventricular arrhythmia. We teased out the role of HPS by disconnecting the HPS network from myocardium at various stages of reentry. Moreover, we varied resistance at the PMJ (R_{PMJ}), and the number of myocytes coupled to a PMJ (N_{PMJ}) during reentry to ascertain how junctional characteristics altered reentry dynamics.

2 METHODS

2.1 3D Anatomical Simulations

Computer simulations were performed using a biventricular mesh of a rabbit heart complete with HPS, which has been used in our prior study (Owusu-Mensah et al. 2021). The biventricular mesh of the rabbit heart and the HPS are described elsewhere (Boyle et al. 2010; Owusu-Mensah et al. 2021). Briefly stated, the biventricular mesh consists of 547,680 myocardial nodes (862,515 nodes including surrounding bath and cavities) and an average internodal spacing of 250 μm. The HPS was a branching network of one dimensional cubic Hermite elements separated by discrete gap junctions which were modeled as fixed resistors. At each endpoint of the HPS, a Purkinje element was coupled to a number of myocardial elements, $N_{PMJ,}$ within a certain radius by a fixed resistance, R_{PMJ}. The current load on each terminal Purkinje element was computed by summing the individual currents flowing into each coupled myocyte and scaling by a load factor to account for sink effects from the surrounding tissue that are not directly coupled. This imposed constraint ensured current conservation at bifurcations and asymmetric propagation across the PMJ (Boyle et al. 2010).

Cardiac electrical activity of the myocardium was governed by bidomain equations (Vigmond et al. 2008) which relates the intracellular and extracellular space through the transmembrane current density. The systems of differential equations were solved using Cardiac Arrhythmia Research Package CARP (Vigmond et al. 2003) – an in silico electrophysiology simulator. Membrane electrical activity in the ventricular myocardium was simulated using Mahajan et. al rabbit ventricular AP model (Mahajan et al. 2008) whereas the HPS was simulated using the AP model developed by Aslanidi et al. (Aslanidi et al. 2010). hERG mutation was incorporated into the AP models of ventricle and Purkinje by completely blocking I_{Kr} conductance in both AP models.

2.2 Reentry Induction Protocol

Reentry was initiated using S1-S2 protocol. Initially, conductivity in the myocardium was reduced to 50% to accommodate the reentrant path for all simulations. After a series of S1 beats at a basic cycle length of 500 ms apart, an S2 stimulus was applied at a quarter region of the right ventricle at a shorter coupling interval that resulted in sustained reentry. Following S2, activity with self-sustained reentry was simulated for 1000 ms. Whilst reentry was sustained, we isolated the HPS from the ventricles at various time points to determine whether and at what time a myocardial reentry can become independent of the HPS(Berenfeld and Jalife 1998). The HPS was isolated from the ventricular myocardium by raising the R_{PMJ} to an extremely high value such that any bidirectional propagation between the Purkinje system and myocardium was not possible. Once the HPS was disconnected from the myocardium, it remained disconnected through the remainder of the simulation.

We conducted another set of simulations to study how the junctional characteristics altered the interaction between the HPS and the myocardium during reentry. This was achieved by varying the N_{PMJ} and R_{PMJ} after a sustained period of reentry. R_{PMJ} was varied in steps of 5 MΩ , starting from 10 MΩ to 25 MΩ. N_{PMJ} was varied from 5 to 25 in steps of 5. We assessed the consequences of R_{PMJ} and N_{PMJ} on reentry dynamics by counting the number of successful antegrade and retrograde propagations. As was done by the authors in (Behradfar, Nygren, and Vigmond 2014) in their study of the role of the Purkinje-myocardial coupling during ventricular arrhythmia, we also considered conduction at the PMJ to be successful when a terminal Purkinje node and 50% of the myocytes coupled to it activated within a reasonable time interval for antegrade and retrograde propagations, otherwise considered failed conduction at the PMJ. Nodal activation was defined as the time at which the transmembrane potential crossed a threshold (-20 mV). Retrograde and antegrade propagation delays were chosen to be 0.96 ms and 9 ms, respectively.

All simulations were performed on High Performance Computing (HPC) facilities of Old Dominion University (ODU) using 40 computing nodes and 2GB of physical memory per node.

3 RESULTS

3.1 Sinus Rhythm

Figure 1 shows the biventricular model of the rabbit heart integrated with HPS which was used to simulate sinus rhythm. Before the application of the stimulus, both the ventricles and the HPS are excitable (Panel a). Sinus rhythm was simulated by applying stimulus to the top nodes of the HPS. The excitation propagated antegradely through the bundle branches to the terminal Purkinje fibers (Panel b). When excitation reached the terminal Purkinje fibers, the myocytes coupled to those fibers are excited (Panel c) which spread the activity to the entire ventricle (Panel d). The ventricles were entirely activated in 86 ms post His activation in the control model – 0% blockade of I_{Kr}. Even in the LQT2 model (I_{Kr} blocked entirely in both the HPS and the ventricles), the time that was taken for the complete activation of the ventricular nodes was close to the control model.

3.2 Isolation of HPS During Reentry

With the HPS isolated, antegrade propagation through the distal Purkinje cells to the coupled myocytes at the PMJs was blocked. Likewise, excitations from the ventricular myocytes at the PMJs were not conducted across the PMJs to the terminal Purkinje cells.

The coupling interval between the S1 and S2 stimuli, which resulted in sustained reentry, was 240 ms (see figure 3A, yellow arrow). After applying the S2 stimulus, we isolated the Purkinje system at five different time points. These were at 243 ms, 279 ms, 210 ms, and 936 ms, respectively, to elucidate our understanding of the contribution of the HPS during reentry. Figures 2 and 3 show a snapshot of the activation sequence and the representative AP of a terminal Purkinje cell and its coupled myocyte, respectively, at different

stages of the reentry with the HPS intact (HPS^{+}) and the HPS removed (HPS^{-}) during reentry at different times.

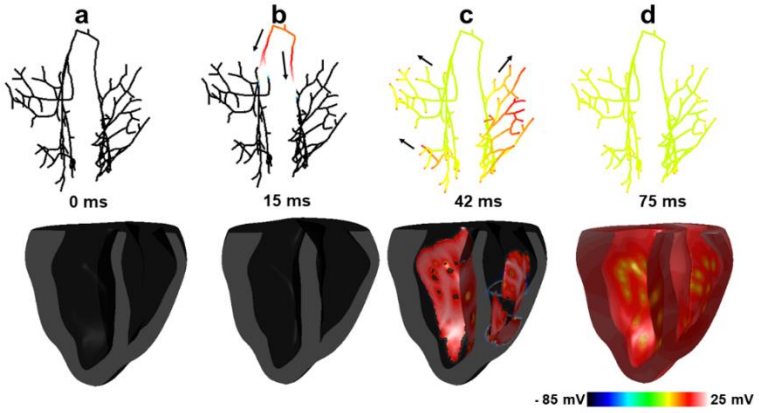

Figure 1: Sequential snapshots of excitations in Control model during sinus rhythm in cross-sectional view of the ventricles (Lower) and the conduction through the His-Purkinje system (Upper)**.**

The activation pattern was different for each scenario, albeit following the simulation with intact HPS until HPS was disconnected. Reentry was terminated shortly after the isolation of the HPS with earliest termination time for reentry coinciding with the earliest time that the HPS was isolated, hinting at the direct involvement of the HPS. When the HPS was disconnected, the transmembrane potential of the terminal Purkinje cells returns to the resting value and fails to excite the myocytes in its vicinity (see figure 3).

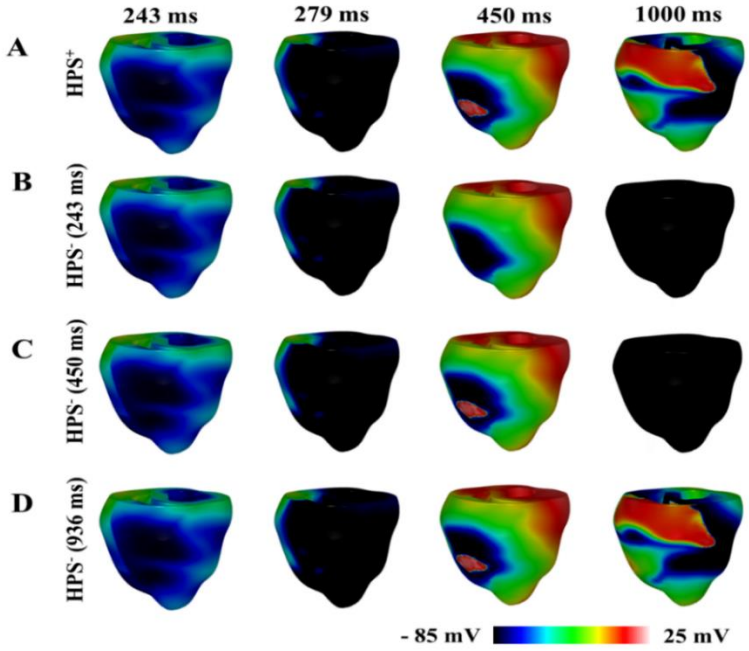

Figure 2*:* Snapshots of the anterior view of the biventricular model during reentry. A) His-Purkinje system (HPS) intact during entire simulation, B) HPS removed at 243 ms, C) HPS removed at 450 ms, D) HPS removed at 936 ms. Intact HPS (HPS^{+}), HPS removed (HPS^{-}).

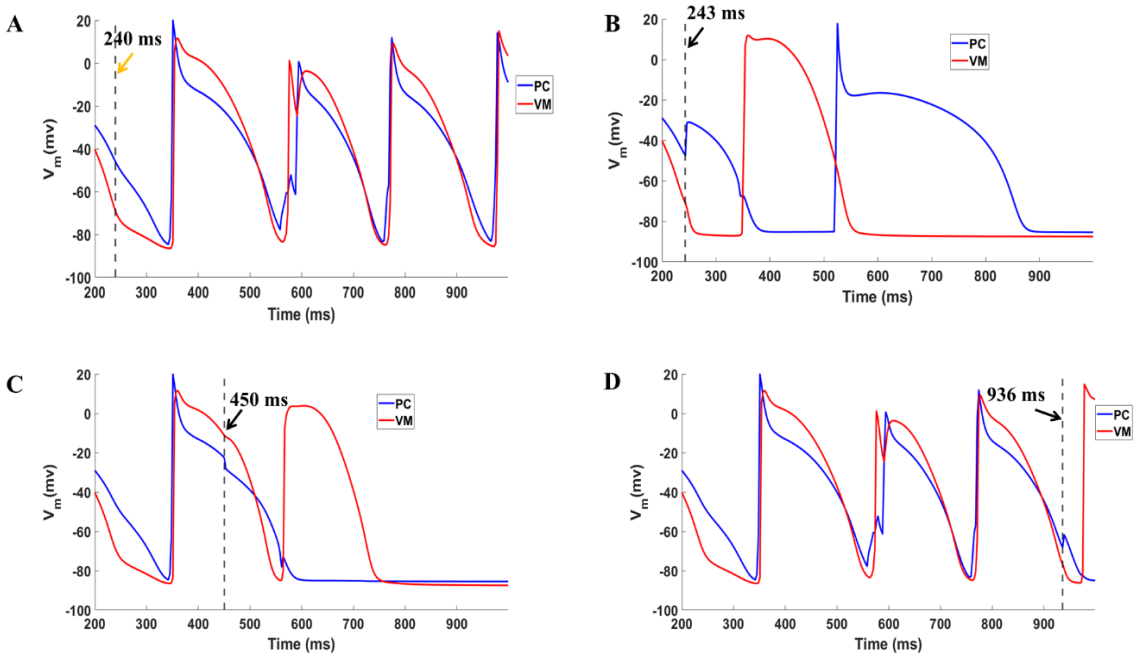

Figure 3: Disconnection of the His-Purkinje system (HPS) from the myocardium at different stages of the reentry. A) Representative action potential (AP) of a terminal Purkinje cell (PC) and one of its coupled ventricular myocytes (VM) with HPS intact during entire simulation, B) Representative AP of a PC and one of its coupled VM with HPS disconnected at 243 ms, C) Representative AP of a PC and one of its coupled VM with HPS disconnected at 450 ms, D) Representative AP of a PC and one of its coupled VM with HPS disconnected at 936 ms. The yellow and black arrow represent the timing of the S2 stimulus and the time HPS was disconnected, respectively.

3.3 Effects of Junctional Characteristics

Figure 4 illustrates the percentage of successful antegrade, and retrograde conduction events for varying values of R_{PMJ} for a given N_{PMJ}. Overall, the percentage of successful antegrade propagation events increased with increasing values of R_{PMJ} for all N_{PMJ}. This can be attributed to the inherently longer AP duration of the cells in the HPS and rapid electrical conduction in the HPS. For a given N_{PMJ}, increasing the R_{PMJ} reduced the percentage of successful retrograde propagation events. Moreover, for a given R_{PMJ}, decreasing the N_{PMJ} values reduced the percentage of successful retrograde propagation events. The number of successful propagation events from the ventricular cells at the PMJs to the terminal Purkinje cells indicates the extent to which ventricular activity drives the HPS. Either increasing R_{PMJ} or decreasing N_{PMJ} yielded similar results.

4 DISCUSSION

In this study, we utilized an anatomically realistic model of the rabbit ventricles integrated with a HPS to mechanistically investigate the contribution of HPS during reentry, which resulted from the complete impairment of the hERG channels. Our modeling study revealed that the HPS played an active role in initiating, maintaining, and terminating reentrant arrhythmias. The sustenance of reentry correlated to the time the HPS was disabled, confirming how ablation of the endocardium has proven to be a potent therapy for ventricular fibrillation (VF). Additionally, the study revealed that the changes in parameters at the PMJs alter reentry dynamics.

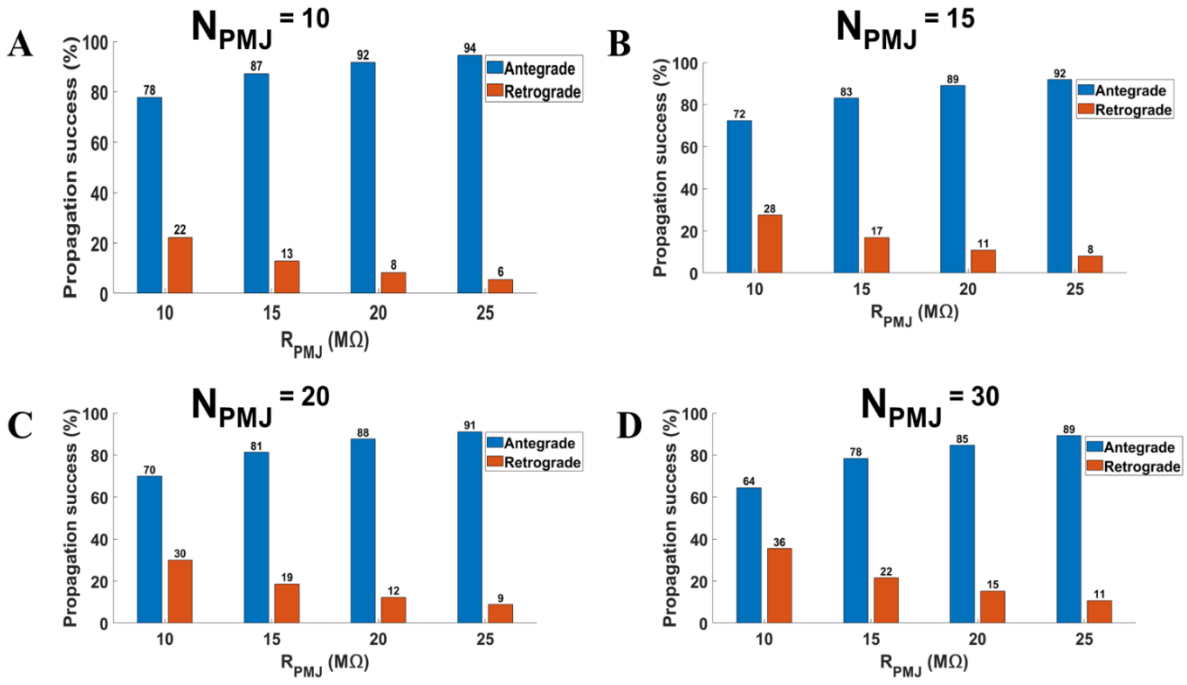

Figure 4: Influence of junction parameters on reentry dynamics. A) N_{PMJ} = 10, for varying values of R_{PMJ}, B) N_{PMJ} = 15, for varying values of R_{PMJ}, C) N_{PMJ} = 20, for varying values of R_{PMJ}, D) N_{PMJ} = 30, for varying values of R_{PMJ}.

We have previously investigated the susceptibility of arrhythmia due to mutation in the hERG gene leading to the partial or complete blockade of I_{Kr} current (Owusu-Mensah et al. 2021). Our previous study extensively focused on the window of susceptibility to reentry in the presence of hERG channel mutation with less emphasis on the influence of PMJ junctional characteristics on reentry dynamics. In the current study, to ensure that the physiological characteristics were accurately created in our model, we replicated the protocol by Boyle et al. (Boyle et al. 2010) to match the literature-reported values for transmission delays at the PMJs and conduction velocity in the HPS. Our model reproduced a more significant delay for antegrade than retrograde transmission, as reported in (Huelsing et al. 1998), as well as the experimentally reported values(Boyle et al. 2010) for conduction velocity in the myocardium and the HPS.

The pathogenic role of the HPS has extensively been discussed in (Haissaguerre et al. 2016). These include the HPS providing accessory pathways for stable reentry within the rich Purkinje architecture in monomorphic tachycardias such bundle branch reentry and as a source of ectopic activity in ventricular tachycardia or VF. In the presented model, the resistance at the PMJ proved to be an essential parameter during reentry as increasing the R_{PMJ} (like decreasing N_{PMJ}) reduced the success rate of retrograde propagation, which is pertinent to the sustenance of reentry. As the R_{PMJ} was increased to an extremely high value, reentry was shortly terminated (see Figures 2 and 3). The termination of reentry due to the removal of the HPS is consistent with work by Dosdall et al. (Dosdall et al. 2008), where chemical ablation of the Purkinje system led to early termination of VF and lower activation rate in dogs. A too high R_{PMJ} value prevents the postjunctional membrane from being charged with adequate charge in a timely manner (Behradfar, Nygren, and Vigmond 2014) to excite the ventricular myocytes at the PMJs.

The study has the following limitations. We prescribed a uniform ventricular and Purkinje action potential across the biventricular model and the HPS. This neglected spatial electrical heterogeneity that has been reported in both the ventricular myocardium(Antzelevitch, 2007; Li et al. 1992) and the His-Purkinje system(Myerburg et al. 1970). In addition, very little is known about the electrophysiology of the Purkinje-

muscle connections. It is proposed that a layer of transitional cells connects the HPS to the VMs at the PMJs; however, the electrophysiology of transitional cells is unknown. The PMJs were modeled as passive resistive junctions.

In summary, our study suggests an active involvement of the HPS in LQT2-mediated arrhythmias. Understanding the role of HPS in LQT2-mediated arrhythmias has therapeutic implications. Despite beta-adrenergic blockade, a common therapeutic intervention for LQTS patients, LQT2 still has a greater incidence of adverse cardiac events in comparison to LQT1, which suggests beta blockers alone may not be sufficient for high-risk LQT2 patients (Cox and Wang 2021). The HPS, with its distinct electrophysiology from surrounding myocytes (Vigmond and Stuyvers 2016), can lead to the designing of HPS-specific drug therapies, which may reduce the adverse cardiac events experienced by LQT2 patients even after the beta-adrenergic blockade and hence reduce mortalities due to LQT2. HPS-specific drug therapies may also be potent in patients with failed catheter ablation or those who are not candidates for invasive therapy. Since optical mapping cannot distinguish Purkinje cells from the surrounding ventricular cardiomyocytes in the subendocardium, this research approach may be used to study anatomic and cellular origins of ectopic activity in arrhythmia syndromes such as Brugada syndrome, short QT, catecholaminergic polymorphic ventricular tachycardia etc.

ACKNOWLEDGEMENT

The study was supported in part by the National Institutes of Health awards 1R15HL145530-01A1, R01-HL156961 and R21-HL153694.

REFERENCES

Antzelevitch, C. 2007. “Role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes”. *American Journal of Physiology - Heart and Circulatory Physiology* vol. 293, pp. H2024–H2038.

Asatryan, B., L. Yee, Y. Ben-Haim, S. Dobner, H. Servatius, L. Roten, H. Tanner, L. Crotti, J. R. Skinner, C. A. Remme , P. Chevalier, A. Medeiros-Domingo , E. R. Behr, T. Reichlin , K. E. Odening, and A. D. Krahn. 2021. “Sex-Related Differences in Cardiac Channelopathies”.*Circulation* vol. 143, pp. 739–752.

Aslanidi, O. V., R. N.Sleiman, M. R. Boyett, J. C. Hancox, and H. Zhang. 2010. “Ionic mechanisms for electrical heterogeneity between rabbit purkinje fiber and ventricular cells”. *Biophysical Journal* vol. 98, pp. 2420–2431.

Behradfar, E., A. Nygren, and E. J Vigmond. 2014. “The Role of Purkinje-Myocardial Coupling during Ventricular Arrhythmia: A Modeling Study”. *PLoS ONE* vol. 9, pp. e88000.

Berenfeld, O., and J. Jalife, 1998. “Purkinje-Muscle Reentry as a Mechanism of Polymorphic Ventricular Arrhythmias in a 3-Dimensional Model of the Ventricles”. *Circulation Research* vol. 82, pp. 1063–1077.

Blackwell, D. J., M. Faggioni, M. J. Wleklinski, N. Gomez-Hurtado, R. Venkataraman, C. E. Gibbs, F. J. Baudenbacher, S. Gong, G. I. Fishman, P. M. Boyle, K. Pfeifer, and B. C. Knollmann. 2022. “The Purkinje–myocardial junction is the anatomic origin of ventricular arrhythmia in CPVT”. *JCI Insight* vol. 7, pp. e151893.

Boyle, P. M., M. Deo, G. Plank, and E. J. Vigmond. 2010. “Purkinje-mediated effects in the response of quiescent ventricles to defibrillation shocks”. *Annals of Biomedical Engineering* vol. 38, pp. 456–468.

Cox, K. O., and B. X. Wang. 2021. “Long QT syndrome type 2: mechanism-based therapies”. *Future Cardiology* vol. 17, pp. 1453–1463.

Dosdall, D. J., P. B. Tabereaux, J. J. Kim, G. P. Walcott, J. M. Rogers, C. R. Killingsworth, J. Huang, P. G. Robertson, W. M. Smith, and R. E. Ideker. 2008. “Chemical ablation of the Purkinje system causes

early termination and activation rate slowing of long-duration ventricular fibrillation in dogs". *American Journal of Physiology - Heart and Circulatory Physiology* vol. 295, pp. 1–16.

Fedida, D., and L. Macdonald. 2016. "hERG long QT syndrome type 2 mutants need more than a chaperone to dance". *Journal of Physiology* vol. 594, pp. 4095–4096.

Haissaguerre, M., E. J. Vigmond, B. Stuyvers, M. Hocini, and O. Bernus. 2016. "Ventricular arrhythmias and the His-Purkinje system". *Nature Publishing Group* vol. 13, pp. 1–12.

Huelsing, D. J., K. W. Spitzer, J. M. Cordeiro, and A. E. Pollard. 1998. Conduction between isolated rabbit Purkinje and ventricular myocytes coupled by a variable resistance. *American Journal of Physiology - Heart and Circulatory Physiology* vol. 274, pp. 1163–1173.

Li, Z. Y., C. Maldonado, C. Zee-Cheng, S. Hiromasa, and J. Kupersmith. 1992. "Purkinje fibre-papillary muscle interaction in the genesis of triggered activity in a Guinea pig model". *Cardiovascular Research* vol. 26, pp. 543–548.

Mahajan, A., Y. Shiferaw, D. Sato, A. Baher, R. Olcese, L. H. Xie, M. J. Yang, P. S. Chen, J. G. Restrepo, A. Karma, A. Garfinkel, Z. Qu, and J. N. Weiss. 2008. "A rabbit ventricular action potential model replicating cardiac dynamics at rapid heart rates". *Biophysical Journal* vol. 94, pp. 392–410.

Meyer, J. S., A. Mehdirad, B. I. Salem, W. A. Jamry, A. Kulikowska, and P. Kulikowski. 2003. "Sudden arrhythmia death syndrome: Importance of the long QT syndrome". *American Family Physician* vol. 68, pp. 483–488.

Moss, A. J. 2003. "Long QT Syndrome". *JAMA* vol. 289, pp. 2041–2044.

Myerburg, R. J., J. W. Stewart, and B. F. Hoffman. 1970. "Electrophysiological propertiesf the canine peripheral A-V conducting system". *Circulation Research* vol. 26, pp. 361–378.

Nakano, Y., and W. Shimizu. 2016. "Genetics of long-QT syndrome". *Journal of Human Genetics* vol. 61, pp. 51–55.

Owusu-Mensah, A., V. Lam, M. Audette, B. Tsevi, and M. Deo. 2021. "In Silico Investigation of Cardiac Arrhythmia Susceptibility in Long QT Phenotype". In *The Thirteenth International Conference on Advances in System Simulation*, edited by F. Herrmann, M. Popescu, and M. Audette, pp. 8–13. Barcelona, Spain, International Academy, Research, and Industry Association.

Priori, S. G., R. Bloise, and L. Crotti. 2001. "The long QT syndrome". *Europace* vol. 3, pp. 16–27.

Roden, D. M. 2008. "Long-QT Syndrome". *New England Journal of Medicine* vol. 358, pp. 1969–1976.

Schafferhofer-Steltzer, I., E. Hofer, D. J. Huelsing, S. P. Bishop, and A. E. Pollard. 2005. "Contributions of Purkinje-myocardial coupling to suppression and facilitation of early afterdepolarization-induced triggered activity". *IEEE Transactions on Biomedical Engineering* vol. 52, pp. 1522–1531.

Vigmond, E. J., R. Weber dos Santos, A. J. Prassl, M. Deo, and G. Plank. 2008. "Solvers for the cardiac bidomain equations". *Progress in Biophysics and Molecular Biology* vol. 96, pp. 3–18.

Vigmond, E. J., and B. D. Stuyvers. 2016. "Modeling our understanding of the His-Purkinje system". *Progress in Biophysics and Molecular Biology* vol. 120, pp. 179–188.

Vigmond, E. J., M. Hughes, G. Plank, and L. J. Leon. 2003. "Computational tools for modeling electrical activity in cardiac tissue". *Journal of Electrocardiology* vol. 36, pp. 69–74.

Zareba, W., and I. Cygankiewicz. 2008. "Long QT Syndrome and Short QT Syndrome". *Progress in Cardiovascular Diseases* vol. 51, pp. 264–278.

AUTHOR BIOGRAPHIES

ANTHONY OWUSU-MENSAH is a Ph.D. student in Biomedical Engineering at Old Dominion University. He holds an MS. in Electronics Engineering from Norfolk State University. His research

interests lie in utilizing high-fidelity numerical models to elucidate our understanding of cardiac arrhythmia initiation and maintenance mechanisms. His email address is aowus003@odu.edu.

OMER BERENFELD is a Professor of Internal Medicine – Cardiology, Biomedical Engineering and Applied Physics at the University of Michigan in Ann Arbor, Michigan. He holds a Ph.D. in Physics from the Tel Aviv University. He is an investigator at the Center for Arrhythmia Research at the University of Michigan and his research interests are in the areas of translational cardiac electrophysiology, arrhythmias, and activation mapping. His email address is oberen@umich.edu.

MICHEL AUDETTE is an Associate Professor in Electrical and Computer Engineering as well as Graduate Program Director in Biomedical Engineering at Old Dominion University. He holds a Ph.D. in Biomedical Engineering from McGill University. His research interests include medical simulation, surgery planning, navigation and robotics, as well as geriatric fall detection. His email address is maudette@odu.edu.