Potential Roles of Purkinje Fibers in Ischemia-Induced Arrhythmias

Teo Puig Walz[1], Luca Azzolin[2], Lucas Berg[3], Enaam Chleilat[1], Hermenegild Arevalo[4]

[1]Institute for Experimental Cardiovascular Medicine, University Heart Center Freiburg·Bad Krozingen and Faculty of Medicine, University of Freiburg, Freiburg, Germany
[2]Institute of Biomedical Engineering, Karlsruhe Intitute of Technology, Karlsruhe, Germany
[3]Federal University of Juiz de Fora, Juiz de Fora, Brazil
[4]Simula Research Laboratory, Oslo, Norway

Abstract

The fast conduction system, in particular the His-Purkinje-System (HPS), is a key element for coordinated electrical activation of the heart. However, it is often omitted in computational studies. We hypothesized that the inclusion of the HPS is necessary when investigating arrhythmia maintenance and termination in an ischemic heart. We used a computational model of regionally-ischemic human ventricles reconstructed from magnetic resonance imaging data, and combined this with a rule-based HPS that produced a realistic activation pattern. Simulations using a high-frequency pacing protocol showed that re-entrant waves through the ischemic region may retrogradely activate the HPS, leading to self-terminating ventricular tachycardia (VT). Simulations without the HPS maintained the ischemia-induced VT, highlighting the role of the HPS in arrhythmia termination. Optical mapping recordings from isolated Langendorf-perfused rabbit hearts during regional ischemia and ischemia-reperfusion are compatible with the conclusions from the in-silico model, showing patterns of re-entry and termination that may be generated from retrograde HPS conduction.

1. Introduction

Computational models are a valuable tool for generating a better understanding of the complex biophysical phenomena associated with normal and pathological conditions because they allow one to perform numerical experiments that would not be possible *in vivo* or *ex vivo*, and at the same time enable a privileged view of underlying mechanisms as all parameters are user-accessible. For a realistic simulation of the heart function, a high level of detail is required. However, frequently, the His-Purkinje-System (HPS) is omitted in order to reduce the computational cost of the simulations. This makes impossible the study of abnormal activation patterns within the HPS [1] or its involvement in re-entry dynamics [2]. In this work we focus on an electrophysiological model of patient-specific ventricles, including a region of myocardial ischemia (MI) and a rule-based generated HPS. We hypothesize that the inclusion of the HPS is especially necessary in computational studies of ischemia-induced arrhythmias.

2. Methods

2.1. Computational Environment

All simulations have been performed using the Cardiac Arrhythmia Research Package [3]. For this study, monodomain simulations have been carried out, and a time-step of 25 μs has been used.

2.2. Patient-Specific Heart

A three-dimensional mesh of post-infarction human ventricles from a patient's magnetic resonance images (MRI) was constructed following the image segmentation pipeline presented by Arevalo *et al.* [4]. The electrophysiological behavior of the tissue was simulated using the ten Tusscher model [5] with its default parameters for the healthy tissue and modified parameters, as presented in Section 2.3, for the MI region. Myocyte orientation was defined with a geometry-driven rule-based approach [6].

2.3. Ischemic Region

The tissue affected by MI was segmented from late gadolinium enhanced MRI data. The whole ischemic region was subdivided into 13 layers of gradually increasing MI to account for central and peripheral ischemia (Fig. 1a-b).

Ischemia was implemented by modeling its main aspects (*i.e.*, hyperkalemia, hypoxia, and acidosis). Increased extracellular K^+ concentration, inhibition of I_{Na}

Table 1. Values of the ischemic parameters for healthy and for most severe ischemic (MI_{max}) region as given by [8].

Ischemia Severity	Healthy	MI_{max}
Hyperkalemia		
$[K^+]_o$ (mM)	5.4	10.4
Hypoxia		
f_{KATP}	0	0.0017
Acidosis		
G_{Na} (%)	100	82.5
G_{CaL} (%)	100	82.5
Tissue Conductivities (S/m)		
Intracellular longitudinal, g_{il}	0.2165	0.1623
Intracellular transverse, g_{it}	0.083	0.0624
Extracellular longitudinal, g_{el}	0.7776	0.5612
Extracellular transverse, g_{et}	0.298	0.2241

and I_{CaL}, and activation of the K^+-sensitive K^+ channel (modulated with a scaling factor $f_{K,ATP}$), as formulated by Ferrero *et al.* [7], have been the modifications from the default ten Tusscher model. To consider the effect of ischemia on gap junctions, tissue conductivities have been modified to match experimental data of conduction velocity (CV) in control and ischemic tissue. The longitudinal CV matched $0.477\ m/s$ or $0.324\ m/s$ in healthy and severely ischemic conditions, respectively, and the transverse CV matched $0.227\ m/s$ or $0.158\ m/s$ in healthy and severely ischemic conditions, respectively. The exact values for the modified parameters for healthy and for the most severely ischemic layer can be found in Table 1, while a linear gradient based on these values has been applied for the intermediate layers.

2.4. His-Purkinje System

The HPS is composed of the His bundle and the Purkinje network. We used a semi-automatic fractal method based on the algorithm developed by Costabal *et al.* [9] to generate a topology of the Purkinje network on the endocardial surface of our mesh. The used parameters are listed in Table 2. The electrophysiological properties of the HPS were incorporated using the Aslanidi *et al.* [10] model for Purkinje fibers, with all parameters as default.

2.5. Pacing Protocol

A pre-pacing stage at the single-cell level is required to bring the model variables close to the limit cycle. This stage consisted of single-cell simulations for each of the 13 ischemic layers, and for the healthy tissue, applying 20 stimuli at a basic cycle length (BCL) of 400 ms. Subsequently, the final states of the model variables of these 14 simulations were distributed across each region, and the tissue-level pacing was started by stimulating from the His bundle at a BCL of 400 ms with a stimulus strength of $500\ \mu A/cm^3$.

Table 2. Parameters used for the generation of the fractal network representing the HPS.

Parameter name	Value
Length of the first branch (mm)	10
Mean length of the branches (mm)	4
Minimum length of the branches (mm)	2
Mean internodal distance (mm)	0.1
Number of iterations	8
Branch angle (degrees)	7
Repulsivity parameter	0.01

2.6. Optical Mapping

Panoramic optical mapping of Langendorff-perfused rabbit hearts allowed us to record sub-epicardial transmembrane voltage (V_m) across the whole heart by means of a voltage-sensitive dye (di-4-ANBDQPQ) used in conjunction with a heart-surrounding LED illumination (640 nm wavelength) [11]. The hearts were perfused globally (*via* the aorta) with an oxygenated physiological saline. At the same time, local cannulation (*via* the anterior branch of the left circumflex coronary artery) allowed perfusing regionally the same solution, or stopping the flow, producing regional no-flow ischemia. After conduction block was achieved, reperfusion of the affected region was performed.

3. Results and Discussion

Constant-frequency pacing of the HPS in our computational model resulted in re-entrant waves through the ischemic region after the second beat (Fig. 1). After the third beat, the re-entrant wave was able to retrogradely activate the HPS in a premature way (Fig. 2a), where one of the Purkinje-Myocyte Junction (PMJ) was activated before it should have been, had the stimulation come from the His bundle. This interplay between re-entrant activation and premature Purkinje stimulation lasted for 4 BCL periods, overriding the default pacing frequency. After this arrhythmic window, the HPS was activated again from the His bundle, terminating the VT.

To asses the importance of the HPS in terminating VT, we performed a simulation in which the HPS was disabled after the initiation of the re-entrant wave. This resulted in a sustained VT pattern throughout the entire simulation time (Fig. 2b), caused by lack of effective synchronised activation of the ventricles that the HPS is able to produce. Without this homogeneous activation pattern, the effective CV of the tissue is drastically reduced. This leads to a reduction of the wavelength (WL) of the electrical activation,

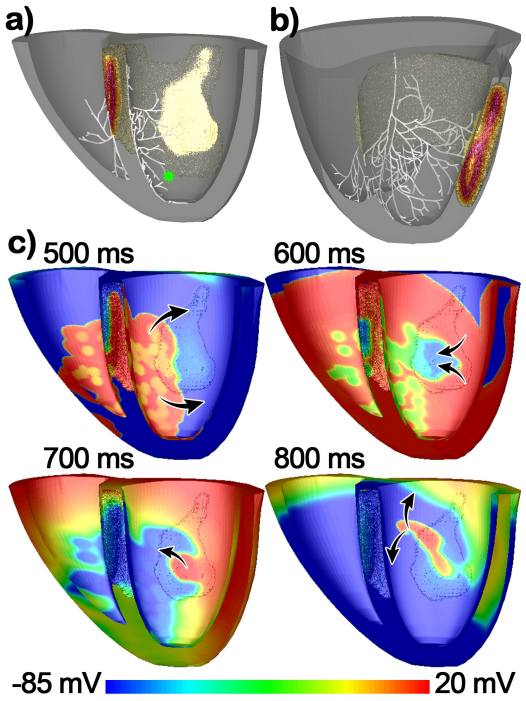

Figure 1. **a)** Frontal and **b)** lateral view of the ventricular model with HPS and cross-section of the 13 ischemic layers that define the ischemic tissue. The red mark in panel (a) identifies the position of the corresponding node for Fig. 2. **c)** Generation of a reentrant wave through the ischemic region after the second beat of HPS pacing at a BCL of 400 ms.

which is proportional to CV and the effective refractory period (ERP), as in $WL = CV \times ERP$. This reduction of WL is known to be a critical factor for allowing a stable rotor of electrical activity to persist for a longer period [12].

Similarly to our simulations, voltage optical mapping of rabbit hearts with regional ischemia shows that re-entrant ventricular activation can produce VT. A representative case of this phenomena is shown in Fig. 3, where sinus-node activation (Fig. 3a) triggers ventricular activation of the healthy tissue without activation of the ischemic region (Fig. 3b). This is followed by a spontaneous wave entering the ischemic region (Fig. 3c-d) which produces re-entry and activates the whole ventricular tissue. The observed pattern is compatible with retrograde activation of the Purkinje network, as indicated by the highly homogeneous activation of the right ventricle (Fig. 3e). Furthermore, in Fig. 3f, the atria are activated prematurely, presumably by retrograde atrioventricular (AV) node conduction, which could be caused by HPS activation (control BCL of 655 ± 31 ms , and BCL of 315 ± 7 ms during re-entry). This re-entrant wave is reproduced in the subsequent activation pattern (Fig. 3g-j).

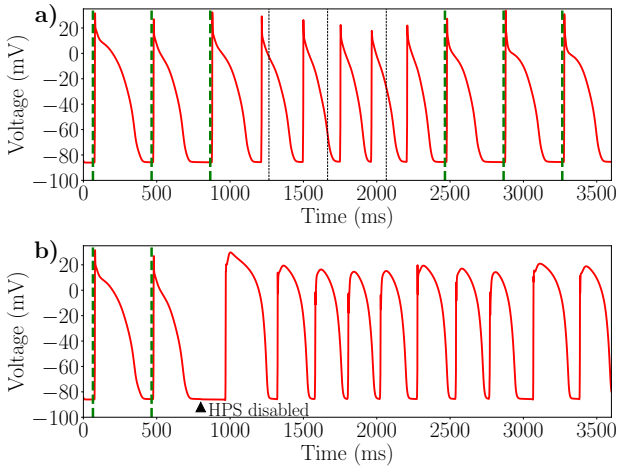

Figure 2. Time evolution of V_m at a node situated next to a PMJ (red mark in Fig. 1a) in a simulation where **a)** the HPS kept being stimulated from the His node at a BCL of 400 ms, and where **b)** the HPS was disabled after the first two stimuli (800 ms). Green dashed lines indicate when the HPS is successfuly stimulated from the His node. The black dashed lines mean that when the His node was activated, the Purkinje network was refractory due to a retrograde activation.

4. Conclusion

We show that the inclusion of the HPS in computational models is essential for studying arrhythmia maintenance and termination in the context of ventricular ischemia. While the Purkinje network was involved in abnormal electrical activity of the heart due to re-entrant activation, it also enabled arrhythmia termination after a certain period of time. The absence of this element of the fast conduction system in the myocardium led to VT being sustained for longer time, due to a lack of synchronized activation of the ventricles that the HPS is able to produce. Observations from optical mapping of isolated rabbit hearts exhibit patterns of re-entry and termination that may be produced by retrograde HPS conduction shown in the simulations. Further experiments targeting ablation of the endocardial part of the HPS could offer better insights of the role of the Purkinje network in arrhythmia termination.

Acknowledgment

This work was supported by the Simula Research Laboratory, the University of Oslo, and the University of California, San Diego, through the Simula Summer School in Computational Physiology 2019. Experimental research benefited from the ERC Advanced Grand CardioNECT (Project ID: 323099, PK). We also thank IEKM members

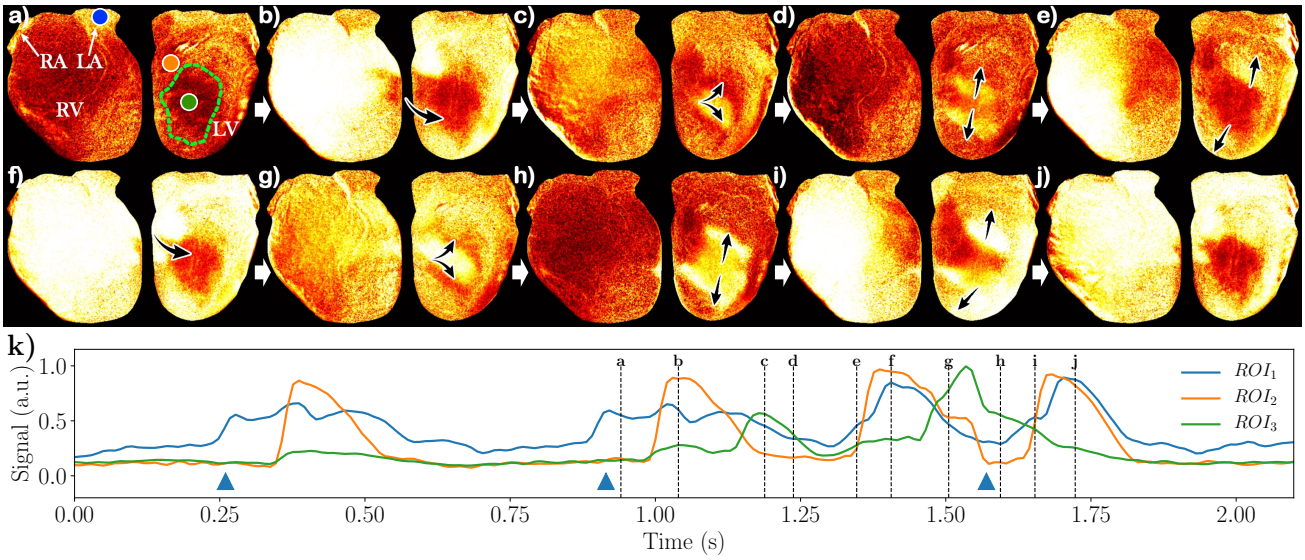

Figure 3. **a-j)** Frames from the panoramic optical mapping recording showing two views of the same heart. The blue circle is the position of ROI_1, the orange circle is ROI_2, and the green circle is ROI_3, representing atrial tissue, healthy ventricular tissue, and ischemic/reperfused ventricular tissue, respectively. The green dashed line marks the border of the ischemic/reperfused region. Black arrows indicate the direction of activation wave propagation. **k)** Optical mapping signal of the three regions of interest (ROI), illustrating also the time points of a-j). Blue pointers indicate expected times for atrial activation based on preceding sinus beats.

for their support, especially Callum Zgierski-Johnston.

References

[1] Tusscher KH, Panfilov AV. Modelling of the ventricular conduction system. Progress in Biophysics and Molecular Biology 2008;ISSN 00796107.

[2] Behradfar E, Nygren A, Vigmond EJ. The role of purkinje-myocardial coupling during ventricular arrhythmia: A modeling study. PLoS ONE 2014;ISSN 19326203.

[3] Vigmond EJ, Hughes M, Plank G, Leon LJ. Computational tools for modeling electrical activity in cardiac tissue. Journal of Electrocardiology 2003;36:69–74.

[4] Arevalo HJ, Vadakkumpadan F, Guallar E, Jebb A, Malamas P, Wu KC, Trayanova NA. Arrhythmia risk stratification of patients after myocardial infarction using personalized heart models. Nature communications 2016;7:11437.

[5] Ten Tusscher KHWJ, Noble D, Noble PJ, Panfilov AV. A model for human ventricular tissue. American Journal of Physiology Heart and Circulatory Physiology 2004; 286(4):H1573–H1589.

[6] Bayer JD, Blake R, Plank G, Trayanova NA. A novel rule-based algorithm for assigning myocardial fiber orientation to computational heart models. Annals of Biomedical Engineering 2012;40:2243–2254.

[7] Ferrero JM, Sáiz J, Ferrero JM, Thakor NV. Simulation of action potentials from metabolically impaired cardiac myocytes. Circulation Research 1996;79(2):208–221.

[8] Dutta S, Mincholé A, Quinn TA, Rodriguez B. Electrophysiological properties of computational human ventricular cell action potential models under acute ischemic conditions. Progress in biophysics and molecular biology 2017; 129:40–52.

[9] Costabal FS, Hurtado DE, Kuhl E. Generating purkinje networks in the human heart. Journal of biomechanics 2016; 49(12):2455–2465.

[10] Aslanidi OV, Sleiman RN, Boyett MR, Hancox JC, Zhang H. Ionic mechanisms for electrical heterogeneity between rabbit purkinje fiber and ventricular cells. Biophysical Journal 2010;98(11):2420–2431.

[11] Lee P, Yan P, Ewart P, Kohl P, Loew LM, Bollensdorff C. Simultaneous measurement and modulation of multiple physiological parameters in the isolated heart using optical techniques. Pflugers Archiv European Journal of Physiology 2012;ISSN 00316768.

[12] Jacquemet V, Virag N, Kappenberger L. Wavelength and vulnerability to atrial fibrillation: Insights from a computer model of human atria. EP Europace 2005;7(s2):S83–S92.

Address for correspondence:

Teo Puig Walz
University Heart Center Freiburg · Bad Krozingen
Institute for Experimental Cardiovascular Medicine
Elsässerstr 2Q · 79110 Freiburg, Germany
teo.puig.walz@universitaets-herzzentrum.de