Vulnerability to Re-entry Arising from LPC-Induced Alterations of Cardiac Sodium Current Kinetics: A Simulation Study

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Abstract

Myocardial ischemia (MI) is the leading cause of morbidity and mortality in the industrialized world. The Gautier et al reported that late sodium current (I_{NaL}) kinetics was remodelled by Lysophosphatidylcholine (LPC) and provided some new insights into the underlying mechanisms of MI. In this simulation study, the kinetics of LPC-induced sodium channels was incorporated into human ventricular cell models and into 1D and 2D transmural tissue model. The simulations found that the increased heterogeneity of repolarisation by LPC significantly prolonged QT interval and might be anticipated to be pro-arrhythmic. Meanwhile, LPC would be anticipated to decrease refractoriness of cells, increase temporal width of vulnerable window (VW) and reduce the wavelength necessary for re-entrant circuits causing an increase susceptibility to arrhythmogenesis. Hence, the I_{NaL} regulated by LPC can be a potential therapeutic target in patients with ischemic heart disease.

1. Introduction

Myocardial ischemia, due to approximately 75% to 80% of all sudden cardiac deaths, is the leading cause of morbidity and mortality in the industrialized world [1]. Although mechanisms and treatment of MI have been studied extensively over the last several decades, it is still far behind the ideal situation. LPC, a hydrolysis product of phospholipid degradation, accumulates rapidly during cardiac ischemia in animal and human hearts. This accumulation of LPC represents a major factor leading to electrophysiological changes including conduction velocity (CV) alterations and cardiac arrhythmias [2]. Experimentally, accumulated LPC during ischemia can remodel sodium channel functions that resulted in a reduction of I_{NaT}, a slow inactivation of I_{NaT} and whilst an increase of I_{NaL} [3]. But it is still unclear how LPC-induced sodium channel alterations at ionic level affect ventricular excitation at tissue level and how it promotes fatal ventricular arrhythmogenesis because of the variety of interventions that ischemia causes cardiac mechanical and electrical dysfunctions [4]. In this present study, similar to the previous researches [5], a cell and tissue computer modeling approach was adopted to determine whether and how LPC-induced sodium channel changes generates an electrical substrate for ventricular arrhythmia. The obtained results explain the underlying mechanism that LPC-induced sodium current reproduces the re-entrant arrhythmia which leads to electrical dysfunction during MI.

2. Methods

The ten Tusscher et al's human ventricular cell models (TNNP models) [6] reproduced epi-cardial (EPI), mid-myocardial (M), and endo-cardial (ENDO) cell action potentials (APs) regarding available human cell and membrane ion channel experimental data and could be used to research heterogeneity of human ventricle [5, 7]. In this study, the TNNP models were modified to incorporate new late sodium current equations (not included in the TNNP models) in order to simulate the effects of LPC on Na^+ channel kinetics [8]. Parameters in I_{NaT} equations were modified regarding the Gautier's experimental data on LPC-induced changes in the kinetics of I_{NaT} that included macroscopic conductance of I_{NaT} deceases 27%, time constant of slow inactivation process increased 200% and the maximal ionic conductance of I_{NaL} increased 250%.

A multicellular model of transmural ventricular tissue was constructed by incorporating the modified TNNP models into a partial difference equation with the form:

$$C_m \frac{\partial V_m}{\partial t} = -I_{tot} + D \cdot \nabla V_m \quad (1)$$

where C_m is cell capacitance per unit surface area ($2\mu F/cm^2$), V_m is membrane voltage, t is time, D is the diffusion parameter modeling the intercellular electrical coupling via gap junction, I_{tot} is the total current across the membrane cell.

A 1D transmural strand was modeled to have a total length of 15.0 mm, which is close to the human transmural ventricular width (~4–14 mm) [9]. In this model, a spatial resolution of 0.15 mm to the whole cell

length and the proration of the heterogonous ventricular cells EPI, M and ENDO was 25:35:40, which was same to other studies [5]. *D* was set to a constant value of 0.054 mm^2/ms to give a conduction velocity of planar wave 0.48 m/s, the maximal speed of conduction along the transverse direction in human myocardium [10]. *D* was homogeneous throughout the strand, except for a 5-fold decrease at the M-EPI border, as previously employed by the Zhang et al.'s model and the Gima et al.'s model [5, 7], in order to simulate a sharp transition of tissue resistance observed experimentally in left ventricular wedge preparation.

A 2D ventricular tissue sheet was modeled by expanding the 1D transmural strand (x-direction is 15 mm) into a sheet with a width of 120 mm (y-direction). The spatial resolution in both x- and y- directions was the same as used in the 1D model.

The pseudo-ECG was computed as an integral of spatial gradient of membrane potential at all positions on the strand from a virtual electrode located in the extracellular space following the methods used by other studies [5, 7].

$$\phi_e = \frac{a^2 \cdot \delta}{4} \int (-\nabla V_m) \cdot \nabla \frac{1}{x - x_0} dx \qquad (2)$$

where ϕ_e represents the unipolar potential recorded at an electrode 2 cm (x_0) from the epicardial end of the strand, δ is the ratio of the extra- and intra-cellular conductivities. *a* is the radius of the fiber and $|x-x_0|$ is the distance from the electrode to any point on the strand.

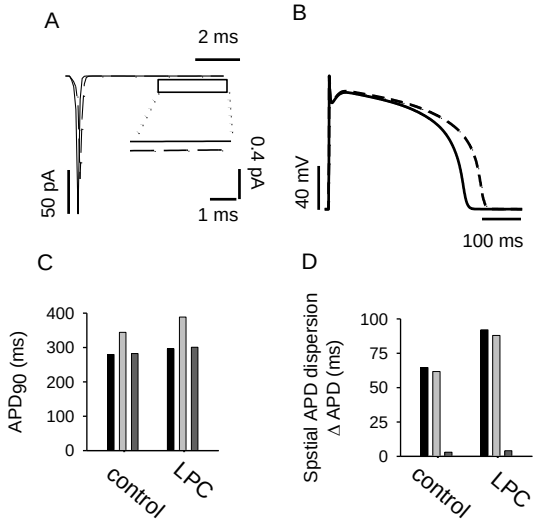

Figure 1. Simulated alternation of I_{Na} currents kinetics and APs under control and LPC conditions.

3. Results

Computational model, which was developed by the Gautier's experimental data on LPC-modulated Na^+ currents, was performed to reproduce the effects of Na^+ channel kinetics and APs by LPC [3]. As illustrated in Fig. 1A, LPC caused a decrease of the peak value of I_{NaT} and a slow inactivation process of I_{NaT} during the upstroke period of AP, and whilst increased I_{NaL} during the plateau of AP (shown in the expanding part of Fig. 1A). During depolarization, the persistent I_{NaL} induced by LPC caused significant prolongation of the AP plateau and augmented the APD_{90} of cells (Fig. 1B). Fig. 1C showed heterogeneous effects of LPC on APD_{90} for EPI, M and ENDO three cell types and the largest effect on the M cell. Meanwhile, LPC also increased spatial APD dispersion across the ventricular wall (Fig. 1D).

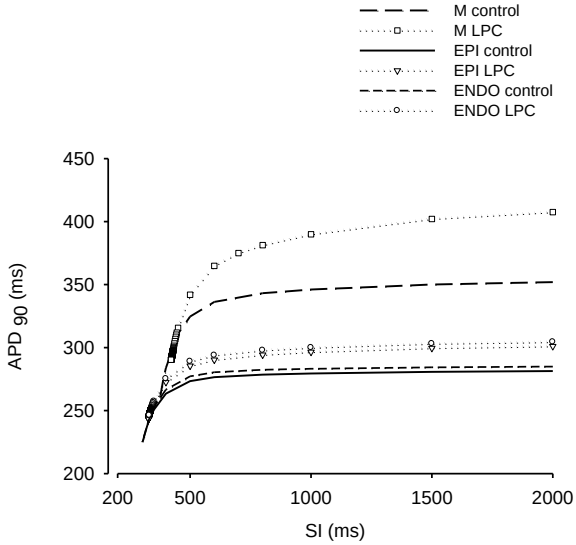

Figure 2. APD restitution curves of three cell types EPI, M and ENDO were obtained by using the S1-S2 protocol.

As indicated in Fig. 2, across the scope of SI studied, APD_{90} was larger in the LPC condition than that in the control condition and APD_{90} prolongation was rate-dependent. We also examined the effects of LPC on transmural electrical excitation and heterogeneity of repolarisation in tissue model since electrical coupling between cells may smooth out transmural electrical differences [11]. Excitation wave propagation across the ventricular wall was simulated using a 1D-strand model. The results of these simulations were shown in Fig. 3. For both control and LPC conditions, a series of stimulus was delivered at the ENDO-end of the strand, the elicited AP propagated towards the M and EPI parts of the strand (in upper panels of Fig. 3A and B). Space ran vertically from ENDO at the bottom to EPI at the top, whilst time ran horizontally from left to right. Membrane potentials of cells along the strand were mapped into a color spectrum ranging from blue for -80 mV to red for +40 mV (see color key). Responding to the excitation propagation in the strand, pseudo-ECGs were computed for control (lower panel in Fig. 3A) and LPC (lower panel in Fig. 3B). The pseudo-QT interval was augmented from 380 ms for control to 402 ms for LPC and T wave amplitude

increased. Whilst QRS wave width and T wave width also increased from ~28 ms (control) to ~34 ms (LPC) and from ~40 ms (control) to ~52 ms (LPC) respectively. To explain this situation, we computed the spatial distribution and gradient of APD_{90} in the intact 1D transmural strand. Fig. 3C showed the repolarization times of all cells on the strand under LPC were later than those under control. It was the reason that QT interval prolongation in LPC was caused by augmented AP of all cells. Spatial gradient of APD_{90} was augmented (Fig. 3D), it could explain augmentation of QRS wave width and T wave width and the increase of T wave amplitude under LPC. In both Fig. 3C and D, a sharp transition of APD_{90} at the M-EPI border was found since the discontinuity of intercellular coupling at the border, which was consistent with the previous experimental and numerical research [5, 7, 9].

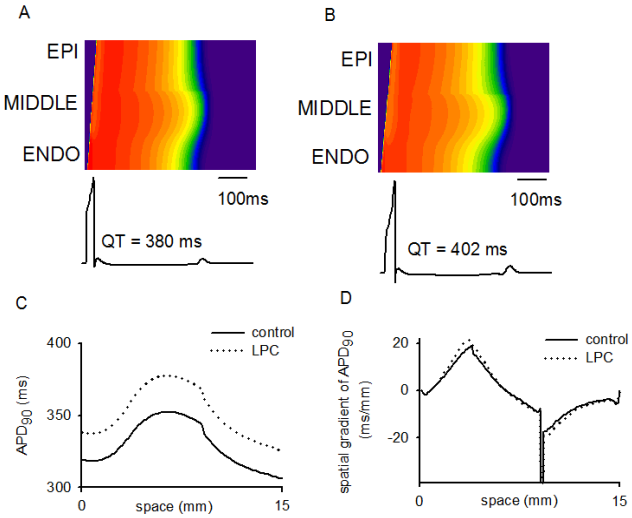

Figure 3. Space-time plot of wave propagation and computed pseudo-ECG and transmural APD_{90} distribution and its spatial gradient in 1D strand.

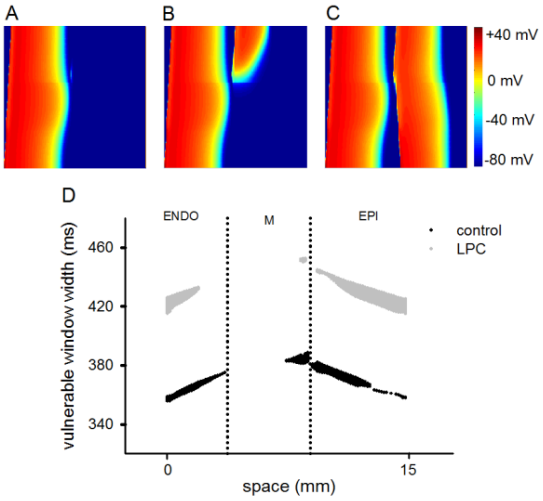

Figure 4. Measurement of temporal vulnerability to re-entry.

In order to investigate whether or not LPC is a potential substrate to increase ventricular arrhythima, a 1D strand model was also employed to quantify the temporal vulnerability of the tissue under both control and LPC conditions. Fig. 4A-C showed the 10th conditioning excitation wave and the response of the tissue to a test stimulus at a different time delay δt after the last stimulus, which resulted in three situations: a bidirectional conduction block (Fig. 4A, δt = 355 ms), or a unidirectional block (Fig. 4B, δt = 360 ms), or bi-directional conduction (Fig. 4C, δt = 365 ms). The width of VW was measured by unidirectional conduction in response to a test stimulus applied to the refractory tail of a previous excitation wave. Fig. 4D showed the measured width of VW under both control and LPC conditions. In control condition, the VW was wide at the EPI part, the ENDO part and the M-EPI border area of the strand. But the middle of M cells part there was no identifiable VW that resulted in unidirectional block. Accordingly, when a test stimulus was applied soon after the previous conditioning excitation wave, middle of M cells part at the stimulus site did not recover enough to evoke full excitation that propagates to the other parts of the tissue and cause bidirectional conduction block occurred. In contrast, when a test stimulus was applied well after the previous conditioning excitation wave, the tissue at the stimulus site recovered enough to generate full excitation that propagates across the whole strand and produces bidirectional conduction as the EPI or ENDO cells have shorter APDs and thus recover earlier than the M cells. Therefore, there was not easy to produce unidirectional conduction in the middle of M cells.

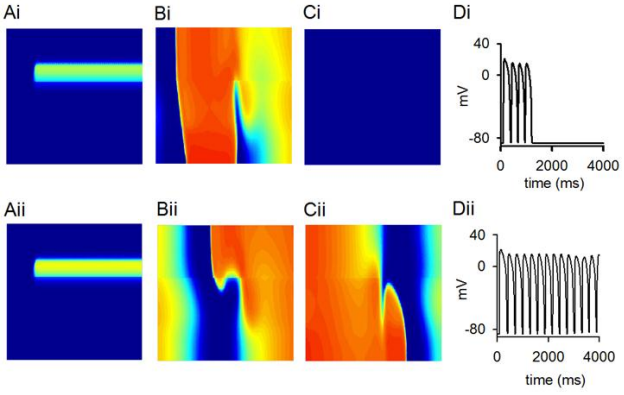

Figure 5. Snapshots of initiation and conduction of re-entry in a 2D model of transmural ventricular tissue under control (Ai-Di) and LPC (Aii-Dii) conditions.

A premature test stimulus during the VW in 2D tissue produced unidirectional conduction leading to genesis of re-entry (spiral wave) as shown in Fig. 5 for control (Fig. 5Ai-Ci) and LPC conditions (Fig. 5Aii-Cii) respectively. For the control condition, the spiral wave was unstable and non-stationary leading to spontaneously terminate at 1.21 seconds. However, the initiated spiral wave in the

LPC condition was found to be sustained throughout the whole period of 4 seconds stimulation, thereby demonstrating an increased susceptibility to arrhythmia.

4. Discussion and conclusions

Much evidence proves that the I_{NaL} in myocytes plays a critical role in the pathophysiology of MI. Experimental research on LPC shows direct facts that Na^+ channels modified by LPC enhance arrhythmia risk in ischemia [3]. However, quantization of I_{NaL} in an intact, blood-perfused heart during ischemia could not be done. Ventricular cellular and tissue computational model provided a valuable and alterative means to investigate these questions. In this present study, we adopted a cellular computational model according the Gautier et al.'s experimental data, incorporated the cellular model into the tissue model to investigate the mechanisms underlying the genesis and maintenance of arrhythmia in ischemia. The major findings of this study are that: (i) implementing changes to I_{NaL} due to the LPC leads to ventricular cell APD_{90} inhomogeneously across the ventricle wall and augments transmural dispersion of APD; (ii) the LPC enlarges the maximal transmural voltage heterogeneity during APs and increases tissue vulnerability to the genesis of unidirectional block by a premature excitation, which favors re-entry. The total influence leads to easily facilitate initiation and maintenance of re-entry in the LPC tissue. These changes combine to generate an electrical substrate favorable to re-entrant arrhythmia in ischemia.

In our simulation study, modifications of sodium channels induced by LPC are causally linked to high risk ventricular arrhythmia during myocardial ischemia. On the one hand, the increased heterogeneity of repolarisation by LPC might be anticipated to be pro-arrhythmic. On the other hand, LPC would be anticipated to decrease refractoriness of cells, which could result in an increased susceptibility to arrhythmogenesis, by increasing temporal width of VW and decreasing the wavelength necessary for re-entrant circuits to become established. LPC, which is the endogenous amphiphilic lipid metabolite that accumulates in ischemic myocardium, represents a major factor causing the electrophysiological alterations that contribute to arrhythmogenesis and the I_{NaL} regulated by LPC can be a potential therapeutic target in patients with ischemic heart disease.

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