Influence of Hydroxychloroquine Dosage on the Occurrence of Arrhythmia in COVID-19 Infected Ventricle

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Abstract

The interaction mechanisms of Hydroxychloroquine (HCQ) in a COVID-19 infected ventricle and its vulnerability to arrhythmogenesis for different dosage levels is not clearly understood. To address this, a 2D transmural anisotropic ventricular tissue model consisting of endocardial, midmyocardial and epicardial myocytes are configured for mild and severe COVID-19 conditions as well as for three dosage levels of HCQ (1 μM, 10 μM and 100 μM). Results show that under control and mild COVID conditions, increasing the dosage of HCQ prolongs the QT interval as well as QRS duration, although under severe COVID-19 conditions, inverted T-waves are observed. In addition, on pacing with premature beats (PBs), it is observed that under all condition, premature ventricular complexes (PVCs) are created at 1 μM and 10 μM HCQ. However, the PVCs are sustained for a longer duration in presence of 10 μM HCQ. ST elevation is observed under mild COVID-19 conditions and 1 μM HCQ and reentrant arrhythmic activity is generated in severe COVID-19 conditions and 10 μM HCQ dosage. Under all conditions, 100 μM HCQ doesn't generate arrhythmia or PVCs in presence of PBs. This in-silico ventricular model indicates that the dosage of HCQ as well as pacing sequence influences the appearance of arrhythmic activity and could help in guiding HCQ therapy.

1. Introduction

Numerous drugs have been attempted to treat the rapidly spreading Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) [1]. Among these, HCQ gained global attention and was studied extensively. Prolonged intake (over 5 years) of HCQ has been linked to developing retinopathy as well as cardiac abnormalities like QRS widening, QT interval prolongation leading to ventricular arrhythmias (Torsade de Pointes (TdP)), hypokalemia and hypotension. Mercuro et al. [2] reported that the median baseline QT_c was 455 ms in 90 COVID-19 patients and increased to 473 ms in presence of HCQ. Those receiving HCQ alone had a 19% QT_c prolongation of 500 ms or more, 13% had a change in QT_c of 60 ms or more and only 1 case of Torsade de Pointes (TdP) was reported. Thus, to date, there is no substantial clinical evidence that provides the detailed mechanism of HCQ's safety or adversity on SARS-CoV-2 infected cardiac tissue, specifically, the target drug concentration that may cause arrhythmia in an infected patient. Wang et al. reported a combination of HCQ and AZM elicited electrical alternans, re-entrant circuits and wave breaks when treating COVID-19 [3]. Further, they reported that different dosages of HCQ blocked the various ionic currents: I_{Na}, I_{CaL}, I_{Kr} and I_{K1} with different intensity.

In spite of tremendous research to find an effective cure for COVID-19, the inhibitory mechanism of a drug and its dosage response on human cells and tissue has not been zeroed down. Such a comprehensive study is difficult to achieve in a short span of time either using in-vivo or clinical studies and can be overcome with the help of computational models, which would elucidate: 1) The effect of COVID-19 on electrophysiological properties of ventricle and 2) supplement the lack of clinical evidence that provides a detailed dosage influence of HCQ on COVID-19 infected cardiac tissue. To address the above gaps, a 2D transmural anisotropic ventricular tissue model framework is used to understand the COVID-19 effect on ventricle. This allows one to understand the tissue level mechanism, including response to pharmacological agents like HCQ. Here, two variations of COVID-19; *mild* and *severe* are explored. Different doses of HCQ and its corresponding changes in ionic currents are included in the tissue to understand its influence. In each case, the variations in the QT interval and T-peak are captured. Finally, the tissue is excited with premature stimuli to analyse and determine under which of the above conditions the tissue becomes pro- arrhythmic. Although earlier studies have established that HCQ induces QT prolongation, TdP arises only in certain scenarios. This study is an attempt to address the possibilities under which arrhythmias occur at the tissue level

in presence of the above mentioned conditions.

2. Methods

The rise and fall of membrane potential in single cardiomyocytes is described by the Ten Tusscher (TP06) model [4]. A stimulus current of amplitude 52 μA is applied for 1 ms is used to excite the cell. The parameters of the cell model and integration scheme are adopted from the study of Priya et al. [5]. The action of various dosages of HCQ on the cardiomyocytes was studied by changing the ionic current parameters [3] as listed in Table 1.

Table 1: Reduction in Ionic Currents for different dosages of HCQ.

Current	HCQ 1 μM	HCQ 10 μM	HCQ 100 μM
I_{Na}	22%	35%	55%
I_{CaL}	12%	12%	40%
I_{Kr}	18%	55%	85%
I_{K1}	10%	20%	80%

As COVID-19 has been linked to causing hypoxemia[6], which in turn leads to hypoxia, this condition was included in the cardiac myocytes by increasing intracellular ATP concentration which would in turn lead to activation of an ATP sensitive potassium current. Using the formulation of Shaw and Rudy [7], ATP activated K^+ current is described by the following formula

$$I_{ATP} = G_{k,ATP} \frac{1}{1 + (\frac{[ATP]_i}{k_{0.5}})^H} (\frac{[K_o^+]}{5.4})^n (V_m - E_k) \quad (1)$$

where $G_{k,ATP}$ is the maximum conductance of I_{ATP} current and has a value of 3.9 nS/cm^2, H and n have a value of 2 and 0.24 respectively. The intracellular ATP concentration ($[ATP]_i$) under normal condition is 6.8 mM, but it decreases to 5.5 mM in *mild* hypoxia and 5 mM in *severe* hypoxia respectively. Similarly, $k_{0.5}$ is 0.042 for normal condition, 0.125 and 0.25 for *mild* and *severe* hypoxia respectively [8]. Henceforth, in this study, hypoxia condition would be referred as COVID-19. As COVID-19 induces fever, this elevated temperature (313.15 K) is also included in the cells of the tissue.

The 2D anisotropic transmural ventricular model of Priya et. al [5] consisting of three layers: endocardial (endo), midmyocardial (mid), and epicardial (epi) cardiomyocytes is adopted. A stimulus is provided at the lower leftmost corner of the tissue to understand the cardiac tissue's spatiotemporal mechanism. The stimuli induces a convex wavefront propagating through the endo, mid, and epi layers, starting from the bottom and ending at the top of the tissue layer. The cell repolarisation first occurs in the epi and endo layers, succeeded by M-cells in the top of the mid-layer.

To investigate the benefits and adverse effects of the dosage of HCQ under control and COVID-19 pathologies, the ion channel variations corresponding to these conditions were included in the cells of the tissue one at a time. A pacing pulse of 75 beats per minute (bpm) is applied in the tissue, and the corresponding voltage propagation is analysed. Further, these activation patterns are validated by synthesising pseudo ECGs for each of the clinical conditions. The variation in the ECG, in particular, QT interval, T-wave morphology and QRS duration are analysed. Furthermore, the tissue is stimulated with premature beats (PBs) (where the consecutive pulses are reduced by a duration of 10 ms) in between the normal beats to study the conditions that can initiate or sustain an arrhythmia.

3. Numerical Results and Discussions

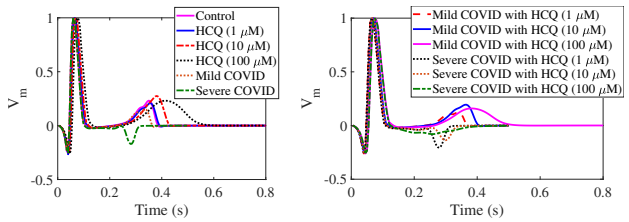
Mild and *severe* COVID-19 ionic current configurations are introduced in the tissue, to study its effect with different dosages of HCQ. The normalized pseudo ECG outcome, is used a) for model validation and b) to give an insight into the mechanism of tissue. Table 2 captures the QT interval, T-peak amplitudes, and QRS duration of these different configurations.

Table 2: ECG Parameters: QT interval, T-peak and QRS duration for different dosages of HCQ in control, *mild* and *severe* COVID conditions.

Dosage (μM)	Condition	QT interval (msec)	T-peak (mV)	QRS (msec)
-	Control	0.350	0.232	0.070
1	Control	0.355	0.208	0.075
10	Control	0.390	0.274	0.075
100	Control	0.505	0.230	0.085
-	Mild COVID	0.325	0.152	0.070
1	Mild COVID	0.330	0.110	0.075
10	Mild COVID	0.365	0.194	0.075
100	Mild COVID	0.450	0.159	0.090
-	Severe COVID	0.275	-0.170	0.070
1	Severe COVID	0.265	-0.206	0.070
10	Severe COVID	0.290	-0.137	0.070
100	Severe COVID	0.345	-0.075	0.080

In comparison to the control ventricle condition, the addition of 1 μM , 10 μM , and 100 μM HCQ, increases the QT interval by 1.42%, 11.43%, and 44.28%, respectively, as shown in Fig. 1(i). However, the T-peak decreases by 10.35% and 0.85% under 1 μM and 100 μM HCQ, but, in 10 μM, it increases by 18.10%. Also, QRS duration increased by 7.14% in both 1 μM and 10 μM HCQ and by 21.4% in 100 μM HCQ. In the *mild* COVID-19 scenario,

the QT interval becomes shortened by 7.14% (0.325 sec) and the T-peak decreases by 34.48% while the QRS duration remains unchanged. In *severe* COVID-19 configuration, the QT interval reduces by 21.48% (0.275 sec) with a negative T-wave peak of -0.17 mV and QT depression. as shown in Fig. 1(iii). This negative T-peak episode might be a representation of ischemia, which is in line with clinical ECG recordings. [9].



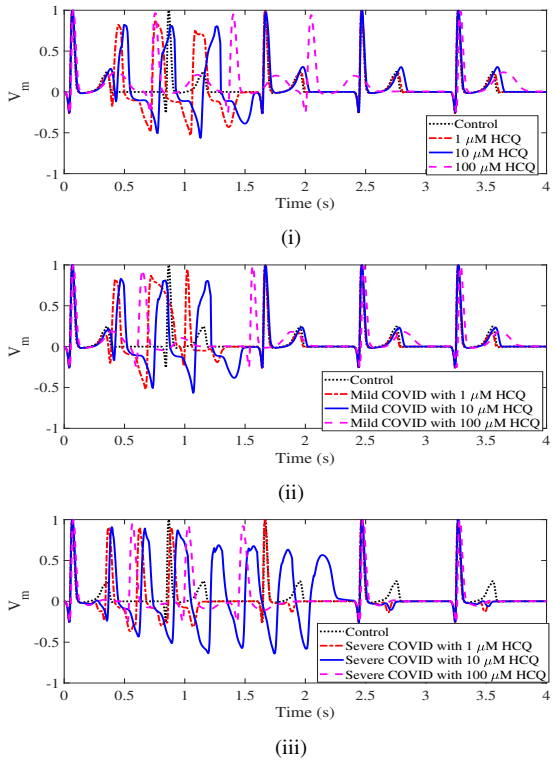
(i) (ii)

Figure 1: Pseudo ECGs generated (i) in control (ii)in *Mild* COVID-19 and *severe* COVID-19 infected ventricle treated with various HCQ doses.

When *mild* COVID-19 condition is treated with 1 μM HCQ, QT interval increases by 1.43% while a double notch T-peak of 0.124 mV and 0.110 mV is seen(Fig. 1(ii)). With 10 μM HCQ, the QT interval prolongs and T-peak increases by 11.42% and 18.10% respectively. When HCQ dosage is 100 μM, the QT interval raises by 35.71% with a 3.02% T-peak increase and 21.4% prolongation of QRS duration. However, in the case of 1 μM and 10 μM HCQ, QRS duration increases by 7.14%. On treating *severe* COVID-19 with 1 μM HCQ, the QT interval reduces by 2.85% in comparison to *severe* COVID-19 and the negative T-peak increases by 15.51%. In contrast, under 10 μM HCQ, the QT interval increase by 4.28%, with a 14.22% reduction in T-peak. When the tissues are treated with 100 μM HCQ, the QT interval prolongs by 20%, with an immense reduction in the T-peak (i.e.) 40.98% in comparison to *severe* COVID-19. Here, the QRS duration is increased by 14.28% in 100 μM HCQ; while remaining unchanged at other dosages.

3.1. Cardiac Tissue Mechanism under Premature Pacing

The research community has well accepted that ionic imbalances at the cellular level lead to disruption in the activation of the natural pathways, thereby giving rise to the reentrant activity, which appears as an arrhythmic event on the clinical ECG. On the other hand, the pacing sequence is also an influencing factor in inducing an arrhythmia. Here, the cardiac tissue is paced with three consecutive premature beats (PBs) with a regular pacing interval of 800 ms (75 bpm). Initialization of first PB in each case is determined by the time the endo cells located at the bottom of the tissue have come out of their refractory state and are re-excitable again. The consecutive beats get reduced by 10 msec. The presence of PBs in *mild* and *severe* COVID-19 setups for various dosages of HCQ are tested to examine arrhythmogenesis occurrence.



(i) (ii) (iii)

Figure 2: Pseudo ECGs generated (i) on pacing the control ventricle with PBs with HCQ inhibition, (ii) on pacing the *Mild* COVID-19 infected ventricle with PBs with HCQ inhibition(iii) on pacing the *severe* COVID-19 infected ventricle tissue with PBs in presence of HCQ

Under control conditons, application of PBs in the presence of 1 μM HCQ or 10 μM HCQ gives rise to premature ventricular complexes (PVCs), as seen in Fig. 2(i) and the regular pacing sequence resumes at 2.4 sec. This appearance of PVC is due to the change in the repolarisation sequence with endo and mid cells repolarising first, followed by the epi cells. On including 100 μM HCQ, the three PBs gives rise to similar ECG complexes (with positive widened T-waves) as that in usual pacing. The regular beat resumes at 3.3 sec after a long pause.

Under *mild* COVID-19, when the first PB is applied; the mid and epi cells in the tissue are yet repolarizing due to the excitation from the previous beat, as a consequence, the wave propagates upward along the endo and mid-layers and lastly enters the epi layer. Succeeding that, the wavefront repolarizes from the endo, mid and epi layer respec-

tively with the cells located at the top of the epi layer repolarizing last, resulting in an inverted T-wave. During the second PB excitation (0.8 sec), the wavefront depolarizes the endo and mid layer but is not able to excite the epi layer cells as they are in a refractory state and this results in an ST-segment elevation in the ECG, as indicated in (Fig. 2(ii). For the last PB, yet another PVC occurs and then regular beats resume at 1.6 sec. In the case of 10 μM HCQ, due to the change in repolarization pattern, PVCs occur, yet they don't lead to the formation of re-entrant patterns. When PB's are applied in 100 μM HCQ setup, ECG complexes with widened T-waves are observed.

In *severe* COVID-19, inclusion of 1 μM HCQ and premature pacing sequence creates ECG complexes with increased negative T-peak amplitude due to the changes in the repolarisation pattern as seen in Fig. 2(iii). The regular pulses resumes after a long pause at 1.6 sec. In contrast, on including 10 μM HCQ and pacing the tissue with the first PB, the M-cells at the top of the tissue are still in the repolarising state. Therefore, the wave travels upwards along with the endo and mid-layer before entering the epi layer. This creates a change in the repolarisation pattern with endo cells repolarising first, followed by mid and epi cells. A similar activation pattern occurs on applying the second PB. When the third PB endures, the epi cells are repolarising; thus, the wavefront travels upwards along with the endo and mid-layer and re-enters the epi layer from the top. Further, the wavefront travels down along the epi layer and re-enters into the mid and endo layer. This reentrant activity creates upward and downward pointing QRS complexes, as shown in 2(iii) and the regular pacing resumes at 2.4 sec following the re-entry termination. In the case of 100 μM HCQ, no arrhythmic activity or PVCs are observed, although flat T-waves occur, representing the appearance of myocardial ischemia event [10] or hypokalemia [11]. The above result infers that an inverted T-wave morphology (representative of ischemia) can be a biomarker for screening *severe* COVID.

4. Limitation and Conclusion

A premature pacing sequence is used to trigger an arrhythmic pattern while other studies report the use of cross-pacing protocol [4] to simulate an arrhythmia in such in-silico models. Our study considers HCQ doses of 1 μM, 10 μM, and 100 μM only as that reported by the clinical study of Wang et. al. The actual percentage variation in ionic currents at other dosage concentrations of HCQ needs to be determined from in-vitro studies, and it would need to be analysed. Inspite of above mentioned limitations, this study is the first complete electrophysiological mechanism of COVID-19 on the human ventricular tissue and its response to treatment with different doses of HCQ. Thus, such computational models strategically allows direct manipulation of ion channels and understanding the influence of these perturbation in COVID-19 infected tissues.

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