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Fatal arrhythmias: Another reason why doctors remain cautious about chloroquine/hydroxychloroquine for treating COVID-19

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BACKGROUND Early during the current coronavirus disease 19 (COVID-19) pandemic, hydroxychloroquine (HCQ) received a significant amount of attention as a potential antiviral treatment, such that it became one of the most commonly prescribed medications for COVID-19 patients. However, not only has the effectiveness of HCQ remained questionable, but mainly based on preclinical and a few small clinical studies, HCQ is known to be potentially arrhythmogenic, especially as a result of QT prolongation.

OBJECTIVE The purpose of this study was to investigate the arrhythmic effects of HCQ, as the heightened risk is especially relevant to COVID-19 patients, who are at higher risk for cardiac complications and arrhythmias at baseline.

METHODS An optical mapping technique utilizing voltage-sensitive fluorescent dyes was used to determine the arrhythmic effects of HCQ in *ex vivo* guinea pig and rabbit hearts perfused with the upper therapeutic serum dose of HCQ (1000 ng/mL).

RESULTS HCQ markedly increased action potential dispersion, resulted in development of repolarization alternans, and initiated polymorphic ventricular tachycardia.

CONCLUSION The study results further highlight the proarrhythmic effects of HCQ.

KEYWORDS Action potential duration dispersion; Arrhythmias; Experimental optical mapping; Hydroxychloroquine; Long QT syndrome; T-wave alternans

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Introduction

The drugs chloroquine (CQ) and hydroxychloroquine (HCQ), a less toxic derivative of QC, are used to treat malaria and autoimmune conditions. They now have been proposed to have antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19) pandemic. Recent *in vitro* studies[1,2] and a small nonrandomized clinical trial of 36 patients from France[3] had promising results and initiated the trend of using CQ/HCQ to treat COVID-19. However, the integrity of the nonrandomized clinical trial has been questioned by the International Society of Antimicrobial Chemotherapy for the trial's unclear inclusion criteria and triage of patients.[4] Although a subsequent smaller randomized clinical trial of 30 patients showed little to no effect,[5] a larger randomized clinical trial of 62 patients showed that HCQ significantly reduced the incidence and duration of COVID-19 pneumonia.[6] These studies do not have sufficient statistical power to unequivocally prove the positive effects of HCQ on COVID-19. Nevertheless, the urgency of the pandemic has resulted in (1) the United States Food and Drug Administration (FDA) issuing an emergency use authorization for CQ/HCQ as treatment of COVID-19, an action that has been criticized by former FDA leaders; and (2) a call by the World Health Organization (WHO) for rapid, large, global CQ/HCQ clinical trials.

Although CQ and HCQ have become the focus as treatment of COVID-19, they remain unendorsed by many physicians because of (1) limited clinical outcome data; (2) availability of other potentially more effective antiviral and interleukin inhibitors, such as remdesivir and tocilizumab, respectively; and (3) potential risk of malignant arrhythmia and sudden cardiac death (SCD) due to QT prolongation.[7,8] In response to the trend of using CQ/HCQ for treatment of

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COVID-19, the Mayo Clinic,[9] the Heart Rhythm Society COVID-19 Task Force in conjunction with the American College of Cardiology and American Heart Association,[10] and other clinicians[11] all independently called for urgently needed guidance when using HCQ alone and in combination with other drugs with regard to arrhythmias.

The most pressing issue is determining the dosage of CQ/HCQ that is effective yet safe, particularly in patients at risk for drug-induced long QT syndrome (LQTS) and SCD.[9–12] This is especially important because HCQ is now being used in combination with other antivirals and antibiotics such as ritonavir, lopinavir, and azithromycin, all of which are associated with drug-induced LQTS.[11] Recent reports have shown direct myocardial involvement in many COVID-19 patients,[13] presumably due to the abundance of angiotensin I converting enzyme 2 receptors on the cardiac cell surface, which is the main entry point of SARS-CoV-2. Evidence of myocardial damage has been described in the form of elevated troponin levels and high inflammatory burden, which can induce vascular inflammation and myocarditis.[13,14] Computational models have proposed that the SARS-Cov-2 envelope protein E' forms a pentameric ion channel, and incorporation of this channel into the cell membrane of cardiac myocytes may contribute to the reported arrhythmic events in COVID-19. Clinically, some patients with severe COVID-19 develop left ventricular dysfunction, cardiogenic shock, and various cardiac arrhythmias.[15,16] Consequently, many COVID-19 patients who already are susceptible to arrhythmias may be at even higher risk for deadly arrhythmogenic effects from COVID-19 drug combination treatments.

A recent clinical trial of 81 patients in Brazil that tested 2 different doses of CQ was prematurely halted because several patients in the high-dose group developed LQTS and experienced malignant arrhythmias, including ventricular tachycardia (VT), within the first 3 days; 11 patients later died within 6 days.[17] Although the precise mechanisms by which QC/HCQ initiates arrhythmia remain unclear, the electrophysiological effects of HCQ have been investigated in isolated mouse and guinea pig (GP) hearts.[18] HCQ primarily blocks the funny current I_f, the L-type calcium current, and the rapid delayed rectifier potassium current I_{Kr}. As a result, the main electrophysiological manifestations of HCQ are sinus bradycardia (Online Figure 1) and repolarization abnormalities (QT prolongation, increased repolarization dispersion), which could lead to torsades de pointes[19] (TdP) and polymorphic VT.[17]

In this study we used optical mapping to demonstrate the arrhythmic effects of HCQ on GP and rabbit hearts perfused with the upper therapeutic serum dose of HCQ (1000 ng/mL).

Methods

Tissue preparation

All experiments conformed to the current Guide for Care and Use of Laboratory Animals, published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996) and were approved by the Office of Research and Integrity Assurance at Georgia Institute of Technology. Animals were lightly anesthetized with ketamine/xylazine/acepromazine (17/9/0.9 mg/kg), then deeply anesthetized with 3%–

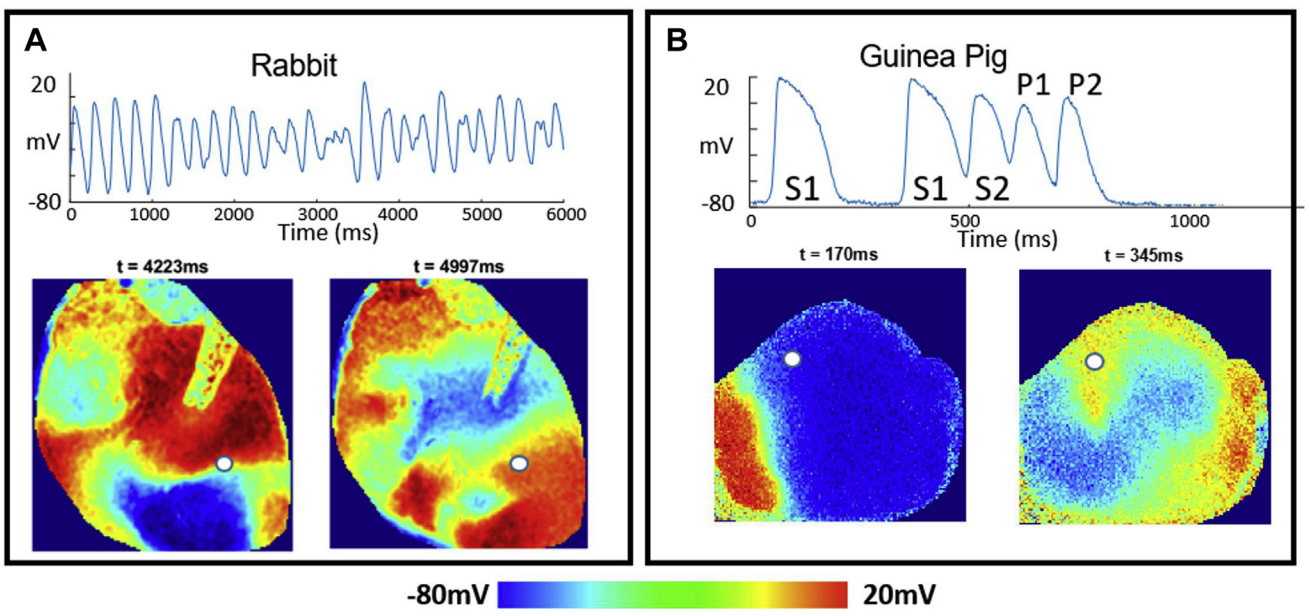

Figure 1 Arrhythmic effects of hydroxychloroquine on rabbit and guinea pig hearts. **A: Top:** Transmembrane voltage signal in time from the region in the heart indicated with a *white dot* in the bottom frames. The voltage signal shows 5 regular activations at 250 ms, followed by initiation of fibrillation, characterized by a fast, disorganized electrical activity signal. **Bottom:** Two frames of the voltage profile on the heart's surface showing multiple fractionated waves driving fibrillation. **B:** Example of arrhythmic ectopic beats following a protocol of two S1 stimuli and a second shorter S2 originating from the apex. **Top:** Voltage signal showing the first 2 beats from a stimulation protocol that emulates a quick change of rate, which creates 2 arrhythmic ectopic (premature P1 and P2) beats. **Bottom:** Optical images showing the initiation of the S2 beat at the apex and then initiation of the first ectopic beat originating from the top center. Color bar indicates tissue polarized (–80 mV) in *blue* and depolarized (+20 mV) in *red*.

5% isoflurane mixed with oxygen for induction and approximately 1%–3% for maintenance of deep anesthesia. Five minutes before euthanasia, heparin 300 U/kg was injected intravenously to prevent vessel blood clots. Hearts were excised via left thoracotomy under deep anesthesia. After excision, hearts were perfused retrogradely via the aorta with warm Tyrode solution (37° ± 0.5°C) for 3 minutes and gassed with a mixture of 95% O_2/5% CO_2 to expel all blood and prepare the hearts for perfusion with cold cardioplegic solution, also gassed with a mixture of 95% O_2/5% CO_2. The Tyrode solution consisted of the following (in mmol/L): for GP: NaCl 124, KCl 4.0 , $NaHCO_3$ 24, $NaH_2PO_4 \cdot H_2O$ 1.2, $MgCl_2 \cdot 6H_2O$ 1.0, $CaCl_2$ 1.8, dextrose 4.0; and for rabbit: NaCl 124, KCl 4.0, $NaHCO_3$ 24, $NaH_2PO_4 \cdot H_2O$ 0.9, $MgCl_2 \cdot 6H_2O$ 0.7, $CaCl_2$ 2.0, dextrose 4.0. Cardioplegic cold solution contained the following (in mmol/L): NaCl 110, KCl 16 , $NaHCO_3$ 10, $MgCl_2 \cdot 6H_2O$ 16, and $CaCl_2$ 1.2; and was used to induce cardiac stasis to protect the myocardium while the hearts were transferred to the optical mapping laboratory (within 15 minutes). For GP hearts, a modified Tyrode solution was used for hypokalemia as described in the Results section.

In the laboratory, the hearts were immersed in a heated oval chamber kept at 38° ± 0.5°C and Langendorff-perfused with Tyrode solution gassed with a mixture of 95% O_2/5% CO_2. Contraction motion was suppressed by (±)-Blebbistatin (Cayman Chemicals, Ann Arbor, MI) at Tyrode concentration of 1.5–2 μM, previously prepared as a stock solution dissolved with dimethylsulfoxide at the concentration of 5 mg/mL. Voltage (Vm)-sensitive dye JPW-6003 (Dr Leslie Loew's group, University at Connecticut, Farmington, CT) was previously prepared as a stock solution dissolved in ethanol at the concentration of 20 mg/mL. For the whole GP and rabbit hearts, 0.4 mg of Vm dye was used. The Vm dye was injected as a bolus in the cannulated aorta over a course of 3 minutes in small injection intervals 15 seconds apart so as not to interfere with the flow rate. The total accommodation time for the heart, including dye staining before the initial measurements were taken, was 30 minutes. Forty-five minutes after cannulation, HCQ was added into the Tyrode solution at a concentration of 1000 ng/mL (upper therapeutic dose of HCQ), previously dissolved in a small volume of Tyrode solution free of organic solvents and stirred for 15 minutes on a hot plate kept at 35°C.

Optical mapping setup

Two red LEDs (each 7 W, center wavelength 660 nm; LED Engin, Wilmington, MA) were used as light sources for Vm dye excitation, which was driven from a stabilized current source (PLUMBUS [Pulsed LUMinos Bimodal Uniform Source]; donated from Aleksa Tech). LED light was collimated with a planoconvex lens (ThorLabs) and bandpass filtered with a 660/10 OD4 filter (Edmund Optics). Emitted florescence was filtered through a 700-nm long-pass OD6 filter (Chroma Optical) placed on the camera side. Fluorescence signals were acquired with an EMCCD camera (Evolve 128; Photometrics) at a resolution of 128 × 128 pixels, digitized at 16 bits at 500 frames per second, and transferred to a personal computer via real-time uninterrupted data transfer. A custom acquisition program was used for camera control.

Stimulation protocol

External bipolar stimuli (World Precision Instruments) 3–5 ms in duration and stimulation current twice the pacing threshold of 3–8 mA were used to investigate the dynamic effect of HCQ. Both before and after HCQ, a down-sweep pacing protocol with pacing cycle length (CL) starting from 400 ms was applied. The CL was gradually shortened in decreasing steps ranging from 5 to 25 ms until conduction block or fibrillation was reached. For each CL, once steady-state conditions were achieved, 20 consecutive beats were recorded. The programming sequence was coordinated with the internal camera trigger clock using an Arduino Uno board, which served to control the onset of each pacing stimulus and to synchronize with the camera. With this method, image stacking could be performed to increase the signal-to-noise ratio and avoid using stronger spatiotemporal filtering, which can oversmooth signals and leave small beat-to-beat action potential differences undetected. During alternans, stacking was performed separately for even and odd beats. To investigate ectopic beats, S1-S2 protocols were run (S1 of 600 ms and 450 ms for rabbit and 450 ms for GP, with S2 varied down until conduction block, fibrillation, or ectopic beat) before and after HCQ.

When fibrillation occurred, defibrillation was performed with low-energy antifibrillatory pacing,[20] which is a low-energy defibrillation method to prevent tissue damage. For the histograms, action potential duration (APD) was calculated at 50% repolarization.

Results

In both preparations, HCQ increased the minimum CL at which pacing the hearts was possible, that is, as the wavelength increased due to the drug's effect, conduction block was easier to elicit for longer periods with the drug, thereby predisposing the heart to arrhythmia. In the GP and rabbit, no fibrillation was obtained without the drug, and it was possible to pace with no arrhythmias at CL as short as 130 ms for GP heart and 140 ms for rabbit heart (Online Video 1). Shorter CLs led to conduction block but no arrhythmias. In contrast, tachycardia/fibrillation not only appeared in both hearts with HCQ, but it was inducible at longer CLs. Furthermore, marked alternans in APD developed with HCQ. Although APD alternans with variations >5 ms from beat to beat can be induced in rabbit ventricles, it is only possible at CL <220 ms. In GP, alternans is not common, but when observed it appears at CL <160 ms. With HCQ, APD alternans readily developed at CL <380 ms in rabbit and <350 ms in GP.

In rabbit, arrhythmias occurred with HCQ at CL <250 ms. Figure 1A and Online Video 2 show the initiation of fibrillation (multiple waves) by conduction block. Figure 2A compares the distribution of APD for CL of 250 ms between

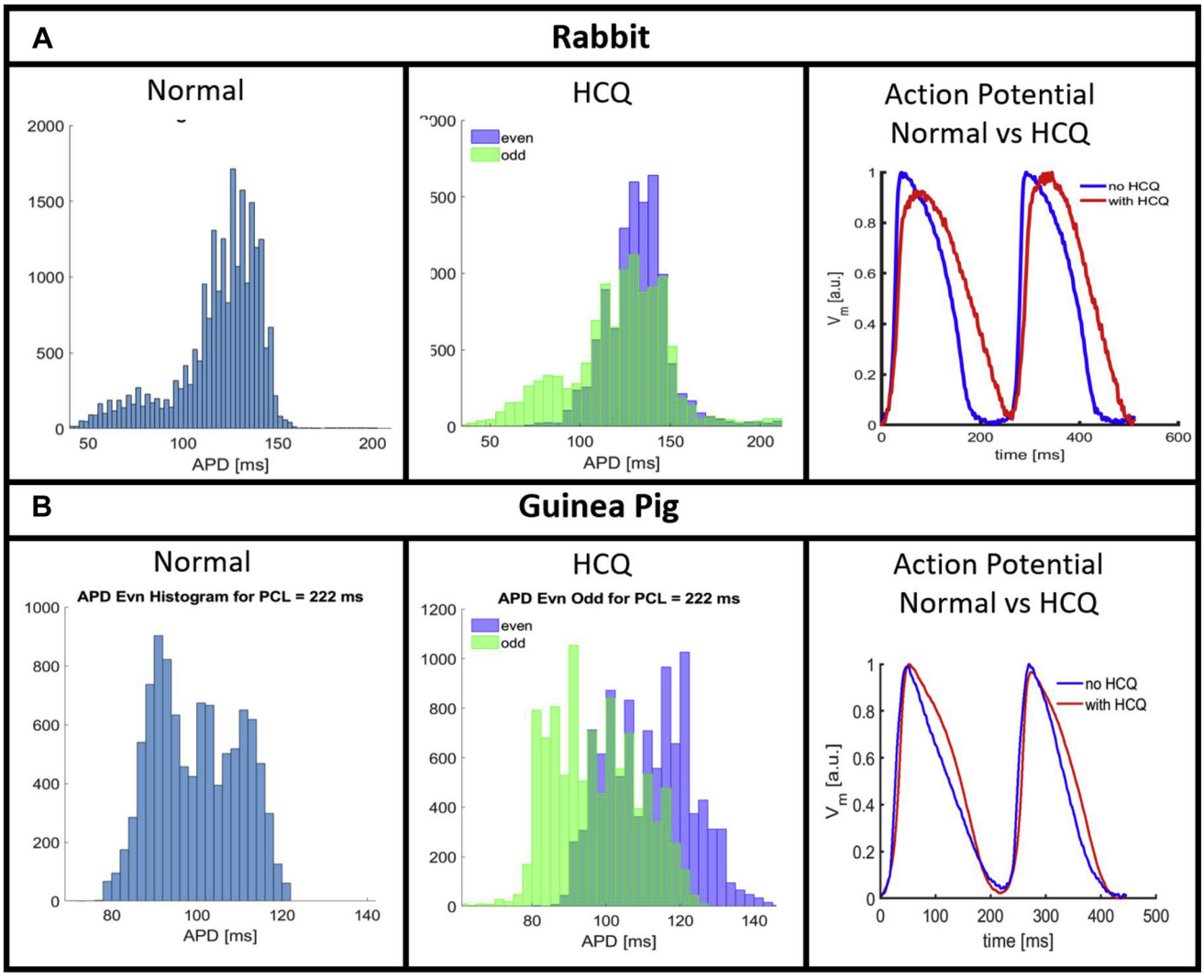

Figure 2 Dispersion of action potential duration (APD) as a result of hydroxychloroquine (HCQ) in rabbit and guinea pig (GP) hearts. Histograms were obtained from optical mapping after steady state was reached for a constant cycle length of 250 ms for rabbit and 220 ms for GP with and without HCQ. As alternans appeared with HCQ, 2 histograms are shown (1 for even beats and 1 for odd beats). **A:** APD distribution in rabbit ventricles with normal Tyrode solution and with HCQ showing an increase in APDmax and alternans from beat to beat. Optical action potentials also show APDmax increase and alternans in duration. **B:** APD distribution in GP ventricles with normal Tyrode solution and with HCQ. Optical mapping signals show similar effect as seen in rabbit. PCL = pacing cycle length.

control and HCQ. The histograms show how APD dispersion increased with HCQ, with APD_{max} prolongation from 155 to 205 ms, and median APD changing from 124 ms to alternating APD values with medians of 125 and 132 ms. Morphologic changes in action potential (AP) also can be observed in the optical mapping voltage trace comparing the normal constant AP with the increased and alternating APs with HCQ. Online Video 3 shows the difference in wave propagation by periodic stimulation between control and HCQ. Without HCQ, continuous pacing is possible even at very short CL of 140 ms with propagation still smooth, whereas with HCQ at even relatively longer CL of 380 ms, large heterogeneities in wave propagation are present. These dynamic heterogeneities promote arrhythmia initiation at CL <250 ms and in some cases complex propagation at CL <350 ms (Online Video 4).

For GP, APD dispersion increased with HCQ, resulting in conduction blocks and arrhythmias initiated at CL <220 ms. Figure 2B shows APD dispersion at this CL (220 ms) without HCQ and the development of alternans with HCQ. With HCQ, alternans changed the normal APD_{min} of 80 ms and APD_{max} of 120 ms to 70 ms and 145 ms, respectively, on alternating beats. Mean APD also changed, alternating between 96 and 112 ms every other beat, representing (220 ms) a decrease and increase in the short and long APD, respectively, compared to mean APD of 104 ms without HCQ. Figure 2B shows the voltage trace and increase in AP duration and alternans with HCQ.

Although there was a large dispersion of APD across the GP heart, spatial alternans mostly developed as concordant alternans (Figure 3), in which APD alternates from long to short values from beat to beat. Only a small region of the

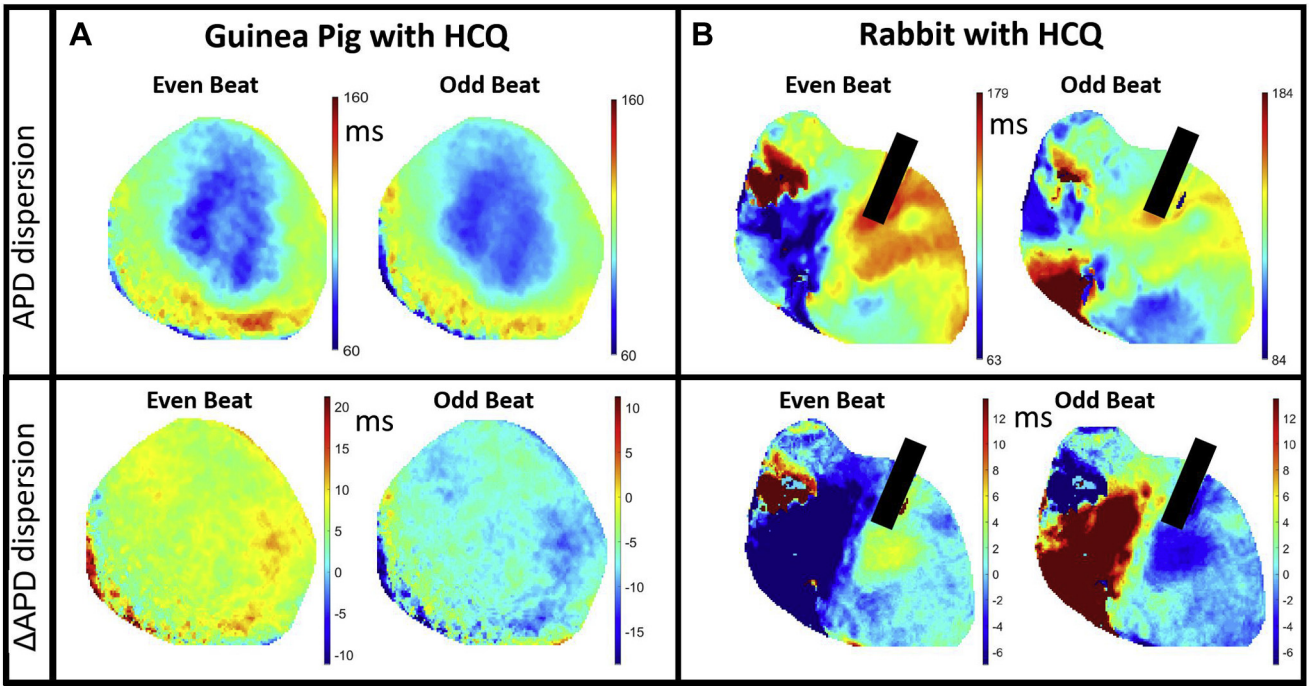

Figure 3 Spatial dispersion of action potential duration (APD) as a result of hydroxychloroquine (HCQ) in rabbit and guinea pig (GP) hearts. Maps were obtained from steady-state activations at a pacing cycle length of 220 ms for GP and 250 ms for rabbit. **Top row:** Distribution of APD for even and odd beats. **Bottom row:** Change in action potential duration (ΔAPD) for even and odd beats. **A:** GP displays mostly concordant alternans in which most of the tissue experiences a short action potential, followed by a long action potential. Only a small region of discordant alternans (DA) with the opposite pattern (long–short) appears in the lower right corner and edges of the tissue. **B:** Rabbit displays marked DA with different distribution of long and short APD on alternating beats. Note that during DA, regions that have a long APD will have a short APD on the next beat, and vice versa. *Black bar* indicates location of the stimulus electrode; data underneath could not be collected.

tissue experienced discordant alternans. However, in rabbit, although the tissue showed a similar range of APDs across the tissue, a more complex spatial pattern developed as alternans was discordant, with some regions of the tissue alternating with long–short APDs and others alternating short–long. The large beat-to-beat changes in APD dispersion due to discordant alternans can be seen in the APD maps and ΔAPD maps (Figure 3).

Although ectopic beats were not observed in rabbit hearts, ectopic beats were seen in GP hearts. Figure 1B and Online Video 5 show 2 ectopic beats generated after 3 stimulations in GP heart. Online Video 6 shows an episode of VT initiation in rabbit heart.

Because hypokalemia has been shown to be prevalent in COVID-19 patients, we tested the effect of HCQ under hypokalemia by switching the Tyrode solution in the GP experiment from normal to lower potassium (from 4 to 2.5 mmol/L) and lower magnesium (from 1 to 0.8 mmol/L). We perfused with hypokalemia Tyrode solution twice, with normal Tyrode solution (washout) in between. In both instances, fibrillation occurred spontaneously under the hypokalemic conditions (the heart was defibrillated when back in normal Tyrode solution), highlighting a possible higher risk of HCQ in patients with hypokalemia and thus the importance of monitoring and treating low potassium levels because they can increase the probability of arrhythmic events.[19]

Discussion

These experiments show that as QT interval/APD increased with HCQ, arrhythmias could be induced at CLs closer to physiological heart rates, thus demonstrating the potential dangers of HCQ. In particular, immediate arrhythmia initiation was observed when hypokalemia was induced with HCQ, but not only in the hypokalemia case. This is important because of particular concern about hypokalemia in COVID-19 disease.[21] Hypokalemia seems to be present in almost all COVID-19 patients,[22] likely due to the interaction of SARS-CoV2 with the renin-angiotensin system (RAS), binding to angiotensin I converting enzyme 2 receptor of RAS and causing prevalent hypokalemia.

With HCQ alone, spatial alternans was observed at longer CLs, including those of normal sinus heart rates without the drug. Although HCQ produces bradycardia that, in principle, may not allow these CLs to be reachable, sympathetic surges can easily lead to sudden increased heart rates that induce pause/bradycardia arrhythmias such as TdP. Furthermore, the increased APD heterogeneity induced by HCQ at bradycardic CLs also showed dramatic anisotropic conduction slowing even before alternans developed. This phenomenon can be seen clearly in Online Video 3. At CL of 380 ms, a marked slowing in conduction velocity is observed in a region of the heart that produces a nonsmooth propagation compared to the case without HCQ at a very short CL of

140 ms. Thus, HCQ induced complex repolarization heterogeneities and a substrate for arrhythmias such as TdP.

Study limitations

The most important limitation is the low number of experiments for rabbit and GP, and we are aware that our results are more descriptive because statistical analysis cannot be performed. However, because our results in normal rabbit and GP hearts compare well with those of other studies in both species,[23,24] and in general when healthy these hearts do not go into fibrillation when slowly paced down (until conduction block) but did so under HCQ, we believe that our study has provided some mechanistic insights. Nevertheless, this study needs to be extended to allow for complete statistical analysis that can solidify the proarrhythmic mechanisms of HCQ as well as the possibility of any differences related to sex, given that female sex is known to be an independent risk factor for developing TdP.

Another limitation of our study is the use of animal models with small hearts and electrophysiologies different from human hearts. A major problem with using small hearts is the difficulty in inducing reentrant tachycardias due to the size mismatch between ventricles and reentrant wavelength. Therefore, a negative result in small hearts is not reassuring for the absence of arrhythmogenicity in humans. However, we observed polymorphic VT with characteristics similar to clinical TdP, which is a finding of concern because typically induction of TdP is easier in humans than in these models.

The most important ion channels in the genesis of TdP are the delayed rectifier potassium channels, especially I_{Kr}. Both rabbit and GP ventricles have dofetilide-sensitive I_{Kr} and are prone to exhibiting repolarization alternans as a result of potassium channel blockade.[25–27] Therefore, these species are commonly used to test for drug-induced repolarization abnormalities[28,29] that could affect humans.

Conclusion

A challenging aspect of COVID-19 treatment with respect to cardiac complications is the use of unusual drug combinations, such as HCQ with antibiotics such as azithromycin, which before the COVID-19 pandemic were rarely used together. The risk profiles of individual drugs with regard to QT prolongation have been characterized, but data on the combinations of those drugs are lacking. Only a few studies, just becoming available,[30] indicate prolongation of LQTS. Although current trials have seldom required discontinuation of therapy, it remains imperative to investigate the safety of potentially effective drugs such as CQ/HCQ and their combinations before their widespread clinical use as treatment against SARS-CoV-2.

Based on the limited and contradictory evidence reported to date, the efficacy of CQ/HCQ against COVID-19 is questionable at best, and the safety is unclear due to the propensity for fatal arrhythmia. Until the results of large, well-designed clinical trials (such as the WHO Solidarity Trial) are available, clinicians have compelling reasons not to treat COVID-19 patients with CQ/HCQ.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at .https://doi.org/10.1016/j.hrthm.2020.05.030.

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