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DRUG-INDUCED VENTRICULAR ARRHYTMOGENESIS IN PATIENTS WITH COVID-19. A LITERATURE REVIEW.

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Introduction **Several existing medications are being repurposed for treatment of COVID-19, including chloroquine and hydroxychloroquine. The use of these medications has been associated with QT prolongation. Their use in patients with COVID-19, magnifies the risk for development of heart arrhythmias.**

Keywords: QT dispersion, COVID-19

Purpose **The aim of this bibliographic research was to perform an analysis of existing clinical reports regarding effects of chloroquine and hydroxychloroquine used in patients with COVID-19 on myocardial repolarization, effects which can be measured on ECG as dispersion of QT interval and manifested clinically as heart arrhythmias.**

Material and methods: **A three-step approach was employed. Firstly, a search of clinical reports in HINARI and PubMed using key words COVID-19 and QT dispersion was performed. Secondarily, selected articles were limited to the English language and human studies. Finally, full texts of all the selected articles were reviewed in details and points relevant to QT dispersion related to use of drugs were extracted. A number of 11 articles was selected for final analysis. Full information regarding age of patients, dosage of drugs used, information about changes in QTc, clinical outcomes were found in 7 articles, which analysis is presented in the table 1 and 2.**

Tab. 1. Risk factors for Torsades de Pointes associated with QTc > 500 ms in patiets with COVID--19

Renal failure
Hypokalemia
Hypomagnesemia
Underlying heart disease: heart failure or myocardial infarction
Hypocalcemia
Hypothyroidism
Advanced age
Bradycardia
Premature contractions producing short-long-short cycles
Impaired hepatic clearance of drugs
Diuretic use
Latent congenital LQTS polymorphisms

Tab. 2. Clinical studies selected for analysis regarding effect of chloroquine or hydroxychloroquine on myocardial electrophysiology and risk for arrhythmogenesis

Authors	Country	Nr. of patients	Average age Male/Female	Dose of chloroquine or hydroxychloroquine	Combination with azithromycin and dose	Changes in QTc interval /maximal QTc	Complication related with QT interval prolongation
Moussa Saleh,et.al	USA	201	58.5 ± 9.1 years M/F: 115/86	Ten patients (5.0%) received chloroquine 500 mg twice daily for one day followed by 500 mg once daily for four days, 191 (95.0%) patients received hydroxychloroquine 400 mg daily for one day followed by 200 mg twice daily for four days.	119 (59.2%) patients received azithromycin 500 mg by mouth or intravenous daily for five days.	QTc enhanced by 19.33 ± 42.1 ms Maximal QTc was 470.4± 45.0 ms.	Seven patients (3.5%) with average QTc of 504.4 ± 39.5 ms required discontinuation of medications. There were 17 instances of new onset atrial fibrillation, 7 patients had monomorphic non-sustained ventricular tachycardia and one patient had sustained, hemodynamically stable, monomorphic ventricular tachycardia. No arrhythmogenic deaths were reported.
Nicholas J.Mercuro et. al.	Israel	90	60.1±16.7years, M/F: 46/44	All patients received hydroxychloroquine, no information about dose.	53 (59%) patients received azithromycin, no information about dose	18 (20%) had posttreatment QTc intervals of 500 ms or more.	Ten patients (11%) stopped taking hydroxychloroquine prior to day 5 of treatment for QTc prolongation caused by premature ventricular contractions and right bundle branch block. One patient who had hydroxychloroquine and azithromycin discontinued because of QTc prolongation (499 ms) developed torsades depointes 3 days later.
Jain et al.	USA	524	68.2±15.2 years M/F: 261/263	All patients received hydroxychloroquine, no information about dose.	Only 3 patients received azithromycin, no information about dose.	20% of the patients showed QT prolongation. Average QTc in patients with QT prolongation was 507.5±28.5ms	In 1/3 of the patients, treatment was discontinued. None of the patients developed torsades de pointes, and only 1 patient had sustained ventricular tachycardia.
Bessiere et al.	France	40	68 (58-74) years M/F: 32/3	All patients received hydroxychloroquine 200 mg, twice a day, for 10 days.	18 patients received azithromycin 250 mg, daily, for 5 days.	Prolonged QTc was observed in 14 patients (36%) (10 with ΔQTc >60 milliseconds and 7 with QTc ≥500 milliseconds) after a duration of antiviral treatment of 2 to 5 days.	17 patients had their drugs stopped because of QTc increase and no patient developed TdP.
Chorin et al.	USA	85	No data available	All patients received hydroxychloroquine 400 mg twice daily on the first day, followed by 200 mg twice daily.	All patients received azithromycin which was given at a dose of 500 mg per day.	QT prolongation was present in most treated patients. In 30% of patients QTc increased by >40 ms, and 11% of patients had severe prolongation (QTc >500 ms).	There were no torsades de pointes events recorded for any patients, including those with a severely prolonged QTc. Four patients died from multi-organ failure, without evidence of arrhythmia and without severe QTc prolongation.
Olivier Voisin et al.	France	50	68 (53-81) years M/F 28/22	All patients received hydroxychloroquine 600 mg/d for 10 days	All patients received azithromycin 500 mg/d on day 1 and 250 mg/d from day 2 to day 5	38 patients (76%) presented short-term modifications of the QTc duration (>30 ms).	Treatment discontinuation was decided in 6 patients (12%), leading to QTc normalization in 5 of them. No deaths and no cardiac arrhythmic events were observed in this cohort.
Möhlmann J.E. et al.	Netherlands	95	65(18–91) years M/F: 63/32	All patients received chloroquine in a loading dose of 600 mg followed by 300 mg twice daily (starting 12 h after the loading dose), with a total treatment duration of 5 days.	no	Mean QTc was 479 (394–564) ms. Mean QTc prolongation was 35 (28–43). 22 patients (23%) had a QTc interval exceeding 500 ms.	No torsade de pointes was observed.

Conclusions:

Medications used in COVID-19 patients have the potential to affect electrophysiology of the heart and can be associated with QT dispersion on ECG. Giving importance to these ECG markers may have a significant contribution in decreasing drug-related arrhythmias in this group of patients.
Chloroquine and hydroxychloroquine particularly when combined with azithromycin increase the QTc in patients.
QTc prolongation is used as a surrogate of risk for torsades de pointes, but the relationship is imperfect. Risk generally increases when the QTc exceeds 500 ms.
The amount of QTc increase varies with drug dose, drug combination, sex, underlying heart disease in addition to COVID-19.