Effects of Chloroquine and Hydroxychloroquine on the Cardiovascular System - Limitations for Use in the Treatment of COVID-19

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Abstract

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are antimalarial drugs, with anti-inflammatory properties that justify their use in the treatment of systemic lupus erythematosus and rheumatic diseases. A pandemic caused by the new coronavirus led the entire world's scientific community to look for drugs already available on the market, capable of exercising beneficial actions in the fight against the disease. Preliminary studies in patients, as well as in vitro studies, suggested possible therapeutic effects associated with the use of HCQ and CQ in the treatment of COVID-19. Despite controversies over the effects of these drugs in combating the "cytokine storm" associated with COVID and the dismal of results in different clinical trials in Brazil, their use has been encouraged and several ongoing investigative studies are underway. In addition to the possible beneficial effects on the prognosis of patients with SARS-CoV-2, such drugs include varied effects on the cardiovascular system, ranging from positive developments related to their vasodilator properties to potential negative effects, such as cardiotoxicity. This work presents the main effects exerted by these drugs on the cardiovascular system, in order to contribute to a scientific discussion about the repurposing of these drugs in the context of COVID-19.

Introduction

COVID-19, a disease caused by the coronavirus (SARS-CoV-2), was discovered in Wuhan, China,

Keywords

and spread rapidly throughout the world (World Health Organization - WHO).[1] Recent reports have highlighted the possible benefits of chloroquine (CQ) and hydroxychloroquine (HCQ) use in COVID-19 treatment.[2] Chloroquine emerged in the 1940s and is clinically used in malaria treatment due to its effectiveness, low cost, safety, and easy manufacture. CQ was synthesized for the first time in 1934, and although its antimalarial properties have been identified, its development was blocked due to the high toxicity observed for this class of drugs. Subsequently, CQ was resynthesized, presenting less toxicity and reported to be superior to sontoquine and quinacrine in malaria treatment.[3] HCQ, clinically introduced in 1955, is an analogue of CQ, also used on malaria treatment, sharing the same mechanism of action. Its clinical indications include skin diseases, sarcoidosis, extra-intestinal amebiasis, chronic Q fever, rheumatoid, and autoimmune diseases.[4,5]

Its antimalarial actions are associated with lysosomal activity and autophagy signaling pathways.[6] CQ and HQ bind preferentially to phospholipids, accumulating in lysosomes which promote changes in pH and direct inhibition of lysosomal enzymes. These effects lead to the impairment of intracellular degradation processes, along with the accumulation of pathological metabolic products (especially phospholipids and glycogen). Histologically, these seem to be vacuolar granule cell mutations and ultrastructural as lamellar membrane inclusion bodies and as "curvilinear bodies" in the cytoplasm.[7]

HCQ has some benefits, such as a reduced incidence of kidney injury and a lower risk of developing serious comorbidities, including venous thromboembolism and pregnancy complications.[8-10] It is considered an essential drug for the treatment of systemic lupus erythematosus (SLE), reducing the impact of the disease and improving

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patient survival. On the other hand, it has a potential retinotoxic effect, a factor which can limit the dose to be used.[11] A previous report indicated that HCQ has less toxic potential than CQ due to the hydroxyl group, which limits the HCQ's ability to cross the blood-retinal barrier.[12]

Investment in the development of malaria treatments has led to a decrease in cases, reducing morbidity and mortality of the disease. WHO estimates that between 2000 and 2010, the incidence of malaria was reduced, and this is due to vector control, improvements in the health system, effective treatments, an increase in notifications, and cases of surveillance.[13] In addition to their antimalarial effects, CQ and HCQ have immunomodulatory actions that are recommended for the treatment of autoimmune diseases. Moreover, it has recently been shown to be effective in reducing cardiovascular risk factors, including hyperlipidemia and hyperglycemia.[14,15]

The adverse effects triggered by the long-term administration of CQ and HCQ were first described in 1948.[16-18] The first publications reported specific toxic effects, such as retinopathy,[19] neuromyopathy,[20,21] cardiomyopathy,[22] and third-degree atrioventricular block.[23] The main reported cardiovascular effects are: vasodilation, hypotension, hypokinesia, and cardiac arrhythmias.[24] The toxic effect is usually dose-dependent. HCQ is melanotropic, and it bioaccumulates in tissues with a high melanin content, such as skin, ciliary bodies, and retinal pigment epithelium.[25] Therefore, allergic patients, psoriasis, porphyria, and alcoholism are more susceptible to cutaneous side effects. HCQ has a toxic potential in pediatric patients,[26] but one study indicated no potential cardiotoxic fetuses after HCQ use during pregnancy.[27]

CQ and HCQ are administered orally, with bioavailability between 70-80%, a long half-life time (30-60 days) and a large volume of distribution (116-285 L/kg).[28] Like all aminoquinolines, metabolites are eliminated through the kidney and liver, thus their excretion decreases in patients with renal or hepatic dysfunction, placing them at high risk for developing toxic effects.[25] Even after treatment is discontinued, they remain detectable in the urine for years.[29]

In general, CQ and HCQ can be considered safe drugs, and side effects are usually mild and transient. However, the therapeutic index is narrow and CQ intoxication has been associated with cardiovascular disorders which can be fatal.[30] Therefore, the use of CQ and HCQ should be restricted and self-medication poses potential risk to patients.

In vitro antiviral activity of CQ has been described since the late 1960s,[31-33] and its role on inhibition of SARS-CoV-1 replication has been shown in Vero E6 cell cultures.[34] In animal models, CQ has presented important effects in a variety of viruses, including human coronavirus OC43,[34] enterovirus EV-A71,[35] Zika virus,[36] and influenza A H5N1.[37] However, CQ was unable to prevent influenza infection in a randomized, double-blind, placebo-controlled clinical trial,[38] as well as having no effects in dengue-infected patients in a randomized clinical trial in Vietnam.[39] CQ was also active in *ex vivo*, but not in *in vivo* studies against ebolavirus,[40,41] Nipah virus,[42] and influenza virus in different animal models.[43] Regarding chikungunya virus (CHIKV), CQ showed promising *in vitro* antiviral activity[44,45] but increased replication of the alphavirus in several animal models.[46,47] These effects are most likely associated with its immunomodulatory and anti-inflammatory properties *in vivo*.[48-50] In a non-human primate model of CHIKV infection, CQ treatment has shown to aggravate acute fever and delay the cellular immune response, leading to incomplete viral clearance.[47] To date, it is important to emphasize that CQ has not been effective in any human acute viral infection.[39,45,47,51,52]

Effects of CQ and HCQ on the Cardiovascular System

The effects of CQ and HCQ on the cardiovascular system are diverse. In the literature, positive effects are reported in patients who used HCQ for SLE treatment, such as a reduction in the incidence of acute myocardial infarction, coronary artery disease, and peripheral arterial disease. These effects are associated with a potential antiplatelet, antithrombotic, and antihypertensive activity of HCQ.[53] In addition, reports indicate that HCQ has a potential to reduce the diabetes development, low-density lipoprotein (LDL) levels, as well as atherosclerosis progression which can contribute to the decrease in cardiovascular events.[54]

However, despite its anti-inflammatory effects and potential antithrombotic action, the literature indicates cardiotoxicity cases with the use of CQ and HCQ. At the molecular level, CQ and HCQ are amphipathic cationic drugs with the capacity to bind to myocyte phospholipids and accumulate in lysosomes, thereby inhibiting their enzymatic activity. This process impairs intracellular degradation, allowing the accumulation of toxic metabolic products.[55] A study conducted by Chatre et al.[56] demonstrated that cardiac disorders associated with HCQ and CQ treatment lead to ventricular

arrhythmias and irreversible damage, which can lead to death. Cardiac side effects are less reported than effects such as retinopathy, but in some cases, they can be severe and irreversible.

Among the main reported effects, conduction disorders and cardiomyopathy, usually with hypertrophy and congestive heart failure, are highlighted. As the clinical characteristics of cardiotoxicity are nonspecific, the identification and monitoring of potentially affected patients is extremely important. Diagnostic confirmation requires histological examination of myocardium associated with electron microscopy. Reports in the literature indicate cases of hypertrophic cardiomyopathy,[57-64] restrictive cardiomyopathy,[65] biventricular dilation,[66-67] and left chamber dilation.[66] The development of cardiomyopathy is recurrent in patients who used CQ and HCQ, and in some cases it is reversed after treatment discontinuation.[60-63,67-69]

Some previous risk factors can increase the incidence of cardiomyopathy, The most important of which are: age, sex, time of use, high doses, pre-existence of heart disease, and renal failure.[69] The HCQ use is associated with diffuse ventricular myocardial thickening, the main secondary myocardial alteration being related to its use.[18,70] In addition, patients with severe heart failure, a worsening of exercise capacity, dyspnea, and angina can also be observed.[68]

In the literature, it is described that the CQ and HCQ use can present long-term effects, even after the diagnosis and immediate suspension of treatment, with clinical and histological characteristics for years.[18,61] Thus, cardiomyopathy is a relevant adverse effect associated with CQ and HCQ treatment. Early diagnosis and periodic cardiological follow-up of the patients are essential for preventing cardiotoxicity and, consequently, the evolution of heart failure.

In addition to morphofunctional changes in cardiomyocytes, conduction disorders have also been reported. Conduction disorders are reported more frequently after chronic treatment with HCQ and CQ, as seen in patients on long-term treatment for SLE, in which cumulative doses are high. However, it is important to note that patients affected by severe form of COVID-19 often have other comorbidities and/or use pro-arrhythmic drugs such as azithromycin, factors that increase the risk of conduction disorders.[71] HCQ and CQ block I_{Kr} potassium channels in cardiomyocytes, which can result in conduction disorders such as: prolongation of the QT interval, atrioventricular blocks, enlargement of the QRS complex, depression of the ST segment, and inversion of the T wave,[72,73] which can result in conduction disturbances, including QT prolongation, atrioventricular block, expansion of the complex QRS, depression of the ST segment, and T-wave inversion.[74] Some reports of HCQ intoxication have been described in the literature, such as the occurrence of sudden ventricular tachycardia after the use of high doses of the drug.[75] As well as quinidine, an antiarrhythmic drug with a chemically similar structure,[76] CQ and HCQ have the potential to cause changes in the QT interval, a risk factor for the development of ventricular tachyarrhythmia.[77-80] Long QT syndrome is an electrophysiological disorder characterized by an increase in the QT interval and abnormalities in the T wave, whose clinical consequences can be dizziness, syncope, and sudden death. [81]

In the literature, cases of syncope and *torsade de pointes* secondary to HCQ-induced cardiotoxicity have been described.[79,82] A study developed by van den Broek et al.[83] demonstrated that CQ treatment was able to generate significant prolongation of the corrected QT interval (QTc) in 23% of the patients with COVID-19 (n = 95). In a cohort study conducted with 201 patients undergoing treatment for COVID-19 with HCQ (95%) and CQ (5%), with or without azithromycin, a high incidence of QTc interval prolongation was observed when compared to the baseline; 8.9% of the patients had a QTc interval above 500ms, of whom 3.5% were indicated for suspension of therapy and 1% were submitted to lidocaine use in order to reverse the condition.[84] A case of *torsade de pointes* was also reported by Szekely et al.[85] in a patient hospitalized with COVID-19, whose QTc interval was excessively prolonged (627 ms; baseline of 462 ms) after the introduction of HCQ therapy. In COVID-19 patients treated with the HCQ and azithromycin association, *torsade de pointes* has been reported.[86,87] To avoid electrophysiological complications, cardiological follow-up during treatment with HCQ or CQ is recommended, with emphasis on electrocardiographic monitoring of the QTc interval.

The occurrence of syncope associated with CQ use may also originate in cases of atrioventricular block or bundle branch block.[88] A retrospective study conducted with 103 patients undergoing treatment for SLE has shown that 18 cases of conduction disorder were identified; 5 cases presented third degree atrioventricular block, of which 4 were using CQ in the treatment protocol.[89] In addition, cases of right and left bundle branch secondary

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to CQ use have also been reported (90,91). The treatment of third-degree atrioventricular block usually requires a pacemaker implant to reverse the condition.[75,88] McGhie et al.[75] observed 453 patients treated with HCQ and CQ drugs, and found, through electrocardiographic exams, that conduction disorders are more prevalent than structural changes, with right branch block being the most common among electrophysiological disorders, followed by bradycardia and first-degree atrioventricular block.

Pulmonary hypertension (PH) is a hemodynamic condition caused by an increase in mean pulmonary arterial pressure, caused by pulmonary dysfunctions or cardiovascular changes.[92] In a model of PH induced in rats, CQ exerted a pulmonary vasodilator effect. The authors suggest that this effect may be related to direct or indirect blockage of voltage-operated calcium channels, store-operated calcium channels, and receptor-operated calcium channels on pulmonary artery smooth muscle cells. The potential therapeutic of CQ in PH is probably associated with the combination of its vasodilator, antiproliferative, and autophagy inhibitory effects.[93]

CQ and HCQ were able to prevent right ventricular hypertrophy and vascular remodeling, as well as improve contractility and cardiac output parameters in PH experimental model. In this model, it was observed that CQ and HCQ treatment inhibited monocrotaline-induced autophagy, preventing the p62 expression, a key protein in autophagy modulation.[94] In addition, CQ has a therapeutic potential in the management of hereditary pulmonary hypertension, since it has the capacity to increase the expression of type II bone morphogenetic protein receptor (BMPR -II) on the cell surface.[95] On the other hand, despite the vasodilatory effects, the cardiotoxicity caused by CQ and HCQ may predispose PH development due to pulmonary circulation overload, as a result of congestion triggered by flow disorders through the left atrium and ventricle.[96]

In a systematic review by Chatre et al.,[56] 86 studies involving patients undergoing CQ or HCQ treatment were evaluated, in which 3.9% developed PH. In addition to this pathology, other important changes were observed, such as: conduction disorder (85%), ventricular hypertrophy (22%), hypokinesia (9.4%), and heart failure (26.8%). Therefore, it was possible to observe that PH, even if present, did not present such a significant prevalence in patients who used the drug. Table 1 shows a compilation of studies that describe electrophysiological and morphofunctional cardiovascular changes in patients after chronic treatment with CQ and HCQ.

Drug Interactions of Clinical Importance Associated with CQ and HCQ Use

Patients with rheumatoid arthritis and SLE are treated chronically with CQ or HCQ. The continuous treatment exposes patients to the development of significant side effects, as well as contributes to an incidence of adverse reactions caused by drug interactions. CQ and HCQ interact with several drugs of clinical relevance, mainly through microsomal enzymes belonging to the cytochrome P450 family (CYP), culminating in the impairment of hepatorenal clearance caused by these therapies.[97] Drug interactions are of great clinical importance, and for this reason, they should receive particular attention. CQ and HCQ are substrates of CYP2D6, CYP3A4, CYP2C8, and CYP1A1, and may change the plasma levels of many drugs and vice versa.[98]

CQ and HCQ interact with clinically important drugs, such as antibiotics, aspirin, paracetamol, cholestyramine, proton pump inhibitors, H2 receptor antagonists, imipramine, methotrexate, cyclosporine, caffeine, metoprolol, among others. Analgesics, often used as acetylsalicylic acid and paracetamol, need more attention. CQ both increases the maximum plasma concentrations of paracetamol[99] and affects its clearance.[100] *In vitro*, HCQ inhibits the activity of plasmatic esterases responsible for aspirin degradation, thereby contributing to increase their circulating levels.[101]

The use of CQ and HCQ associated with drugs used in the treatment of cardiovascular diseases requires adequate monitoring in order to minimize the possible cardiotoxic effects inherent to the combination therapy. CQ can increase the plasma digoxin concentration up to 4-fold and precipitates clinical manifestations, such as arrhythmia and cardiotoxicity.[102] Additionally, metoprolol can present changes on its plasmatic concentration when used concomitantly with HCQ. This interaction occurs through competition for the same metabolizing enzyme of both drugs, CYP2D6, resulting in an increase of concentration and bioavailability of metoprolol.[103]

Due to the pandemic caused by COVID-19, several clinical studies have been conducted in order to characterize a safe and effective therapy for the treatment of this disease. Some already published studies emphasize that HCQ associated with azithromycin presents potentialized effects, exerting promising actions in the COVID-19 treatment.[104,105] In addition, a study by Fantini J et al.[106], using a dynamic molecular simulation technique, demonstrated a synergistic antiviral effect

Table 1 – Electrophysiological and morphofunctional cardiac alterations in patients after chronic treatment with chloroquine (CQ) and hydroxychloroquine (HCQ)

Reference	Therapeutic Indication	Electrophysiological alteration	Morphofunctional alteration	Intervention
Nord et al., 2004	SLE	Atrial flutter	LV and RV dilation; LVPW hypokinesia; (EF: 20%)	HCQ suspension; radiofrequency ablation; cardioverter implantation.
Nord et al., 2004	SLE	VPC	LA e LV dilation; global hypokinesia; SAH and PH (EF: 23%)	HCQ suspension
Lenfant et al., 2020	SCLE	CD	cardiomyopathy (LV hypertrophy)	CQ suspension
Cervera et al., 2001	SLE	Complete heart block	Restrictive cardiomyopathy (EF: 36%)	Pacemaker implantation; CQ suspension
Gentille et al., 2011	SLE	Complete heart block	-	Pacemaker implantation; CQ suspension
Lee et al., 2010	RA	Sinus arrest; junctional rhythm	Hypertrophic cardiomyopathy; (EF: 44%)	Pacemaker implantation; HCQ suspension
Chatre et al., 2016	SLE	-	Cardiomyopathy; (LV hypertrophy)	HCQ suspension
Yogasundaral et al., 2018	PR	Bifascicular block	Cardiomyopathy; (EF: 60-67%)	CQ suspension
Baguet et al., 1999	SLE	Heart block; PR interval prolongation	Cardiomyopathy; (LV hypertrophy) (EF: 45%)	Pacemaker implantation; CQ suspension
Naqvi et al., 2005	SLE	-	Cardiomyopathy; (LV and RV hypertrophy) (EF: 60%)	Pacemaker implantation; CQ suspension
Dogar et al., 2017	RA	-	(EF: 55%)	HCQ suspension
Cotroneo et al., 2007	SLE, RA	Incomplete RBBB	Cardiomyopathy; (LV hypertrophy) (EF: 40%)	HCQ suspension
Reffelmann et al., 2015	RA	Complete RBBB; sinus arrest; junctional rhythm	Cardiomyopathy; (LV hypertrophy); PH	CQ suspension; Pacemaker implantation
Abid et al., 2020	SLE	Complete heart block	-	Pacemaker implantation; HCQ suspension
Cubero et al., 1993	SLE	Complete heart block	Atrial dilation; (LV and RV hypertrophy) (EF: 42%)	-
Reuss-Borst et al., 1999	RA	Complete heart block	-	Pacemaker implantation
Reuss-Borst et al., 1999	SLE	Complete heart block	-	Pacemaker implantation
Saussine et al., 2009	SLE	Complete heart block	-	Pacemaker implantation; CQ suspension
Saussine et al., 2009	SLE	LAHB; LPHB; Complete heart block	hypokinesia	Pacemaker implantation
Costedoat-Chalumeau et al., 2007	SLE	Complete heart block	LV and RV enlargement; (EF: 24%);	Heart transplantation; CQ suspension
Aslanger et al., 2008	HPul	Complete heart block	-	Pacemaker implantation
Chen et al., 2006	SLE	TdP; PR interval prolongation with VPC	-	HCQ suspension

Abbreviations – CD: conduction disorder; EF: ejection fraction; HPul: pulmonary hemosiderosis; LA: left atrium; LAHB: left anterior hemiblock; LPHB: left posterior hemiblock; LV: left ventricle; LVPW: left ventricle posterior wall; PH: pulmonary hypertension; PR: palindromic rheumatism; RA: rheumatoid arthritis; RBBB: right bundle branch block; RV: right ventricle; SAH: systemic arterial hypertension; SCLE: subacute cutaneous lupus erythematosus; SLE: systemic lupus erythematosus; TdP: torsades de pointes; VPC: ventricular premature contraction.

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of HCQ combined with azithromycin in the COVID-19 treatment. However, both treatments are able to promote prolongation of QT interval, which trigger refractory ventricular arrhythmia, even when used alone.[79,107] Chorin et al.[86] reported cases of *torsade de pointes* in patients with COVID-19 who were treated with the HCQ and azithromycin association. In addition, they observed a prolongation of the QTc interval above 500 ms in 23% of the cases (n = 211). The French Pharmacovigilance Database reported that 14% of the adverse effects linked to the association of HCQ with azithromycin corresponded to blockage in the cardiac conduction system (n = 120).[87] Although CQ and HCQ show *in vitro* antiviral activity against COVID-19 in some studies, there is no robust evidence to demonstrate the clinical benefit of combined HCQ and azithromycin therapy in reducing the mortality of hospitalized patients with a severe form of COVID-19. Moreover, the deleterious effects on the cardiovascular system are notorious and should not be neglected.[65,108]

Other important drug interactions are associated with the widespread use of CQ and HCQ with immunosuppressive drugs in the treatment of rheumatoid arthritis and SLE, such as methotrexate and cyclosporine. CQ and HCQ impair the methotrexate absorption by pH variation, thereby reducing its oral bioavailability, which contributes to sub-therapeutic effects of methotrexate.[109,110] CQ and HCQ may also increase cyclosporine plasma levels, enhancing the risk of nephrotoxicity. Thus, cyclosporine use should be monitored during combination therapy in order to avoid potentially toxic effects.[111,112] CQ is also able to reduce the bioavailability of some classes of antibiotics, such as penicillin and quinolones, limiting their therapeutic effects.[113,114]

On the other hand, drugs that raise gastric pH can reduce the CQ and HCQ bioavailability, such as proton pump inhibitors and H2 receptor antagonists, restricting their therapeutic effects.[115] Since a range of drug interactions involving the long-term use of CQ and HCQ and these drugs have a low therapeutic index, it is extremely important to monitor patients who continuously use these drugs to ensure both clinical efficacy and safety.

Effects of Chloroquine and Hydroxychloroquine on other Systems

Retinopathy is an adverse effect widely described as a consequence of CQ and HCQ use. However, the mechanism involved in toxicity associated with retinopathy is not fully understood.[116] Retinal toxicity can cause irreversible visual loss. The result of the analysis of 2,361 patients using HCQ revealed an overall prevalence of 7.5% of toxicity in patients treated for more than 5 years and 20% in those treated for more than 20 years.[117] The main identified risk factors were doses of HCQ above 5mg/kg or CQ above 2.3mg/kg, duration of use for more than 5 years, previous renal failure, use of tamoxifen, and macular disease.[116,118]

Ponticelli and Moroni[119] observed that 10% of patients treated with HCQ developed corneal deposits which were dose-dependent, transient and reversible. However, in most cases, the retinopathy was irreversible. It is important that patients treated with HCQ and CQ receive a warning of the risk of toxicity as well as a periodic evaluation. The most common visual symptoms include reading and sight difficulties, photophobia, and visual blur.

The multifocal electroretinography (mfERG) provides objective documentation of visual functions, and exerts an important role in screening and evaluation in order to manage the discontinuation of treatment. However, further studies are needed to define the relationship between the time of physiological evolution and structural abnormalities. In addition, the sensitivity and specificity of mfERG can be assessed when compared to automated visual fields, fundus autofluorescence imaging, and optical coherence tomography.[120] A recent study showed that retinopathy progresses for 3 years even after HCQ treatment suspension. In this same study, they have observed more severe changes in patients who received doses above 11mg/kg/day. Thus, it is extremely important to periodically evaluate patients who use these drugs in order to diagnose the early stages of development of retinopathy and provide a detailed analysis of risk and progression of visual loss in these patients.[25]

Undesirable dermatological events include such pathologies as psoriasis, alopecia, itching, skin pigmentation and mucous membranes, photosensitivity, and skin rashes.[121] Another adverse effect reported is myopathy, the main symptoms of which are muscle weakness, increased levels of muscle enzymes, electromyographic changes, and histological lesions.[122]

Chloroquine and Hydroxychloroquine in the COVID-19 Treatment: Impact on the Cardiovascular System

Diseases that affect the cardiovascular system represent a risk factor for patients with COVID-19, as well as diabetes, pulmonary disorders, and obesity.

Therefore, such individuals are more susceptible to developing the severe form of the disease.[123-125] On its surface, SARS-CoV-2 expresses proteins that interact with its receptor, ECA2.[126] Tissues that widely express this receptor are more vulnerable to viral invasion, such as lungs, cardiovascular system, intestine, kidneys, central nervous system, and adipose tissue.[127,128]

Patients with COVID-19 have shown a higher incidence of acute heart failure,[123,129] and critically ill patients are more susceptible to present cardiovascular damage.[123,130,131] Mehta et al.[132] have observed that patients with COVID-19 have a cytokine production profile similar to secondary hemophagocytic lymphohistiocytosis (sHLH), which is associated with poor prognosis. This phenomenon has been described as "cytokine storm", characterized by an unregulated response of type 1 and type 2 auxiliary T cells.[123] This "cytokine storm" is marked by exacerbated increase in interleukins (IL), such as IL-1, IL-6, and IL-7, granulocyte colony stimulating factor (G-CSF), protein 10 induced by γ-interferon (CXCL10/IP-10), monocyte chemotactic protein 1 (MCP-1), inflammatory macrophage protein 1-α (MIP-1α), and tumor necrosis factor-α (TNF-α). Mortality predictors from a recent retrospective, multicenter study of 150 confirmed cases of COVID-19 in Wuhan, China, included elevated ferritin (mean 1297.6 ng/mL in non-survivors vs. 614.0 ng/mL in survivors; p <0.001) and IL-6 (p <0.0001), suggesting that mortality may be associated with hyperinflammation promoted by the virus.[131]

Cardiac injury is related to direct damage caused by viral replication and cytokine storm. In addition, respiratory dysfunction and hypoxia generated by COVID-19 can also cause damage in cardiomyocytes.[123,133,134] Clerkin et al.[135] reported that 7% of infected patients developed myocardial injury, diagnosed through echocardiographic examination or electrocardiogram, and presented elevated troponin I levels. Considering that the cardiovascular system is directly affected by SARS-CoV-2 infection, therapy with drugs that have a cardiotoxic potential becomes even more contraindicated.

Although the *in vitro* antiviral effects of CQ have been demonstrated by reducing the viral replication of SARS-CoV,[34,136] inhibiting HIV replication,[50] in addition to in vivo antiviral effects reported in an H1N1 animal model,[37] clinical studies demonstrate controversial data regarding its effects on reducing viral loads in humans. Engchanil et al.[51] reported that CQ was not effective in improving clinical, immunological, and virological parameters in HIV-infected pediatric patients, and tended to cause an increase in undesirable gastrointestinal events. In a double-blind randomized study with 307 hospitalized adults with dengue fever, it was observed that CQ was not able to reduce viremia,[39] and actually increased the incidence of adverse gastrointestinal effects. A study performed by Borges et al.[137] showed that CQ apparently reduced symptoms related to the disease, but was not able to decrease the time infection caused by dengue virus. CQ treatment in Chikungunya infection was evaluated in a double-blind, placebo-controlled study developed by Lamballerie et al.,[45] which indicated that CQ did not reduce viral loads and in fact increased the incidence of arthralgia when compared to the placebo arm. The work performed by Gautret et al.,[104] reported in March 2020, demonstrated that HCQ exerts beneficial effects in COVID-19 treatment. However, the study showed several limitations that were clarified by Toumi and Aballea,[138] such as a reduced number of enrolled patients, outcome measures, and a lack of homogeneity in both the control and treated groups. These questions compromise comparability between arms and lead to a deficiency in the control of the occurrence of type I statistical error and other inconsistencies in the protocol study.

Due to the widespread use of HCQ in hospitalized patients with COVID-19 without robust evidence to support its use, several clinical trials have been performed to confirm or refute its efficacy and safety in these patients. A randomized, controlled, multicenter clinical study conducted in China, evaluated 150 hospitalized patients with moderate and severe COVID-19. HCQ treatment did not promote additional beneficial effects in eliminating viral loads when compared to standard treatments, in addition to causing significant adverse events.[139] An observational study by Geleris et al.,[140] evaluated 1,446 patients with COVID-19 and found that HCQ treatment neither reduced nor increased the risk of intubation or death in the evaluated patients. Another observational study evaluated the HCQ effectiveness in 181 patients admitted with COVID-19 pneumonia who needed oxygenotherapy. In this study, the use of HCQ was not indicated for these patients, since treatment did not reduce the length of hospital stay nor the mortality rate. In addition, 10% of patients treated with HCQ have presented significant electrocardiographic changes and discontinued treatment.[141] Finally, a recent clinical study conducted with 1,438 hospitalized patients diagnosed with COVID-19, has shown that HCQ therapy is not associated with a reduction in mortality by COVID-19.[52]

Given the unproven efficacy, it is possible to promote cardiotoxicity in isolated or combined therapy with other drugs commonly used in the treatment of COVID-19, in addition to the fact that patients infected with COVID-19 may have direct damage in their cardiovascular system. It is important to evaluate critically and ethically if the CQ and HCQ use is necessary as a therapeutic approach to SARS-CoV-2 infection,[142] considering all the risks associated with their use (figure 1).

Conclusion

Chloroquine and hydroxychloroquine represent drugs with a potential benefit in the treatment of several pathologies, presenting important anti-inflammatory and immunomodulatory actions, with their pharmacological effects evidenced in the chronic treatment of autoimmune diseases. However, their side effects should not be overlooked, especially ophthalmic and cardiovascular effects, which can lead to vision loss and cardiotoxicity. This article describes relevant negative impacts of these drugs on the cardiovascular system. The performance of several clinical trials with CQ and HCQ in COVID-19 patients leads to an ineffectiveness of these drugs. The absence of efficacy, in addition to potential deleterious effects on the cardiovascular system, suggest that

this pharmacological approach should be used with caution, especially due to the large number of patients with COVID-19 who have pre-existing cardiovascular disorders.

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Conception and design of the research: Brazão SC, Autran LJ, Lopes RO, Scaramello CBV, Brito FCF, Motta NAV. Writing of the manuscript: Brazão SC, Autran LJ, Lopes RO, Scaramello CBV, Brito FCF, Motta NAV. Critical revision of the manuscript for intellectual content: Brito FCF, Motta NAV.

Figure 1 – Associated risks with CQ and HCQ use in the treatment of patients with COVID-19.
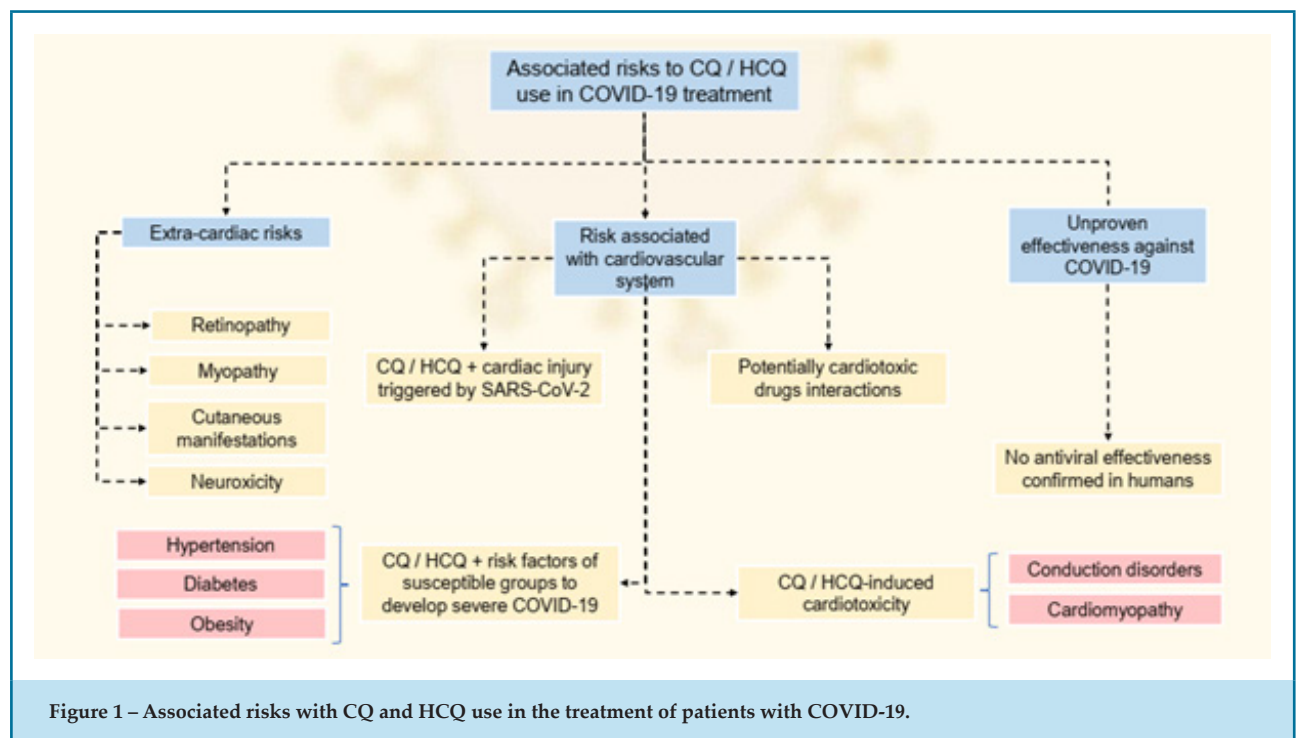
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