

Severe Cardiovascular Complications of COVID-19: a Challenge for the Physician

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Introduction

Since December 31, 2019, when China reported the appearance of cases of acute respiratory failure caused by a new species of coronavirus, SARS-CoV-2, which causes the disease called COVID-19, almost 20 million cases were confirmed, causing 726 thousand deaths worldwide.¹ In Brazil, on August 8th, 2020, there was approximately 3 million cases and 100 thousand death by the disease.¹

Its rapid spread, its high potential for hospitalization, and its high lethality, especially in the most fragile groups such as geriatric patients and those with comorbidities, particularly cardiovascular ones, make this pandemic a challenge never faced by modern medicine. To date, we have no specific medication that has effective and safe results for the treatment of COVID-19. The scientific community has sought to research drugs with therapeutic plausibility, and controlled and randomized studies are underway. Many therapeutic proposals are based on in vitro experiments. The medications used are described in case records, with no solid scientific evidence for their use, and with a

high probability of causing damage due to their adverse effects alone or in combination.²

In this context, multiple clinical and experimental studies with cell cultures mainly from China, suggested that chloroquine, a drug that has been used for more than 70 years in the treatment of malaria, and as an anti-inflammatory in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, could play a role in the treatment of COVID-19.³ Currently, more than 80 studies using chloroquine and hydroxychloroquine alone or in combination with other drugs were registered worldwide, seeking to transpose the benefits described in cell cultures to human studies.²

Both chloroquine and its more recent analogue, hydroxychloroquine, have a direct effect on the replication of SARS-Cov-2 in experimental studies, reducing the efficiency of virus binding to ACE2 (angiotensin-2 converting enzyme) and increasing the lysosomal pH, preventing the virus-cell fusion proces.⁴ One of the main problems to be faced in these studies is the complex pharmacokinetics of 4-aminoquinolines, which makes it difficult to extrapolate concentrations of culture media to doses in humans.⁵

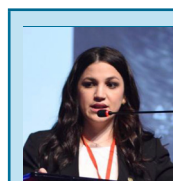
Studies from China, with a questionable methodology, for not presenting a description of the results, study protocols, doses, side effects, and statistically significant benefits between the groups, made their use in the treatment of COVID-19 quite debatable. One of these

Keywords

COVID-19/complications; Pandemics; Betacoronavirus; Cardiovascular Diseases/complications; Arrhythmias, Cardiac; Stroke Volume; Death, Sudden; Chloroquine; Hydroxychloroquine; Azythromycin.

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studies with a small number of patients showed that chloroquine was associated with a higher percentage of clinical and virologic cure and started to be adopted in that country in the treatment of COVID-19.⁶

Its use was approved by the United States Food and Drug Administration (FDA) with the blessings of President Donald Trump,⁷ although numerous side effects have been described such as fulminant liver failure, left ventricular failure, and arrhythmias (especially when prescribed in association to azithromycin).⁸

Azithromycin is a macrolide antibiotic widely used in clinical practice for upper and lower respiratory tract infections. It has also been studied for its *in vitro* effect against the Zika and Ebola viruses, and is often used to prevent serious respiratory tract infections when administered to patients suffering from viral infection.⁹⁻¹¹ As a complementary therapy in the treatment of SARS-Cov-2, a small French study with 36 patients, with non-randomized controls from another cohort, reported that hydroxychloroquine with or without azithromycin reduced the detection of viral RNA in respiratory swabs, the most significant effect being associated with azithromycin.¹²

Currently, the FDA recommends the use of these medications “out of compassion”, alone or in combination, until we have scientific evidence of their effectiveness.⁷ The Brazilian Ministry of Health, as of March 25, 2020, started to adopt chloroquine as an adjuvant therapy in the treatment of severe forms exclusively, without other support measures being neglected in its favor.¹³ Worldwide, this association has been used off-label in severe cases, outside of research protocols, but there is still no scientific evidence.

Although the safety profiles of chloroquine / hydroxychloroquine and azithromycin are suitable for isolated use in chronic diseases, both medications have the potential to prolong the QT interval, which greatly increases the risk of ventricular tachycardia (mainly Torsades de Pointes), bradycardia, and sudden death, especially in scenarios of systemic inflammation caused by epidemic respiratory viruses.¹⁴⁻¹⁶

It is observed that the highest incidence of events occurs in people with other predisposing factors, such as long QT syndrome, structural cardiovascular diseases, or the use of other drugs that prolong QT.¹⁷ In addition, it was demonstrated that approximately 20% of patients with COVID-19 have myocardial injury, 10% have myocarditis, and 10 to 30% evolve with shock,¹⁸ which

would multiply the probability of adverse effects in a pro-inflammatory and pro-thrombotic environment. These patients possibly have greater substrates for arrhythmia and electrolyte disturbances, and still in the critical phase of the disease, most patients admitted to intensive care units are treated with multiple combined therapies, such as vasoactive amines, diuretics, and serotonin 5-HT₃ receptor antagonists, among others.

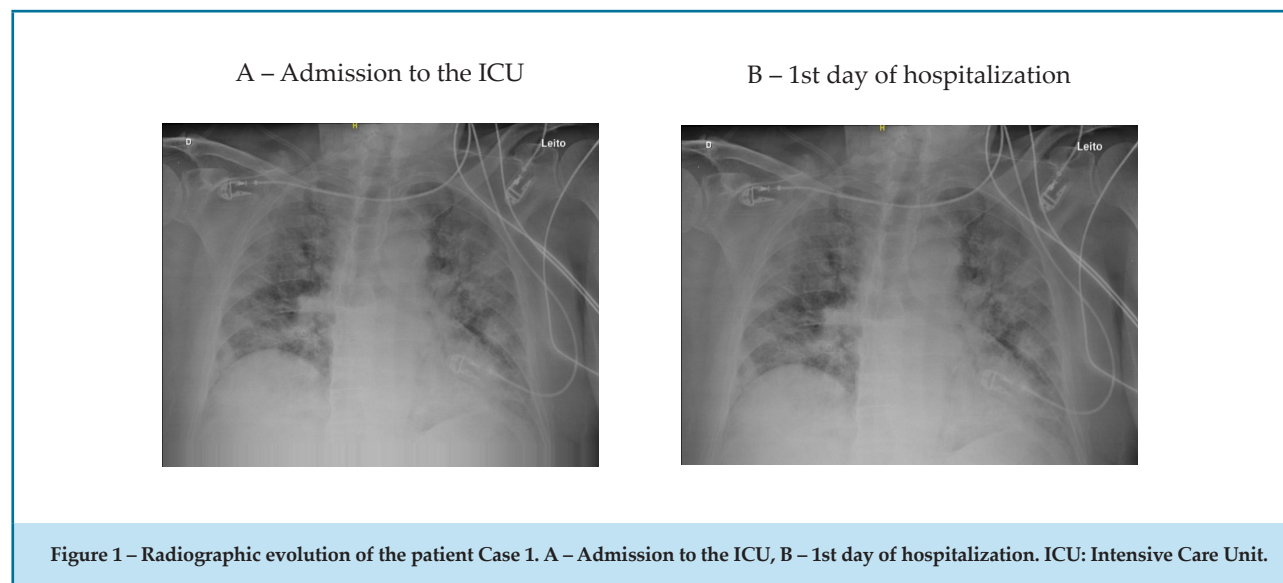
Both chloroquine / hydroxychloroquine and azithromycin have a known effect in prolonging the QT interval by blocking IKr (hERG) channels.¹⁹⁻²⁰ Concomitant use was uncommon until the current pandemic. There are reports of prophylactic use in malaria and some sexually transmitted diseases and little data on increasing the QT interval with their combined use.²¹ Furthermore, although drug-induced QT is a reliable indicator of high-risk Torsades de Pointes (TdP), this correlation is not linear. Some drugs increase the QT interval without increasing the risk of sudden death, while others increase the risk of TdP without necessarily extending the QT interval.²²

Next, we describe 2 cases of patients admitted to the Intensive Care Unit with COVID-19, who used the association of hydroxychloroquine sulfate or chloroquine diphosphate with azithromycin, and presented with severe cardiovascular complications. The aim was to illustrate the observations described above, with emphasis of the lack of safety of combination therapies not tested in clinical trials capable of generating robust scientific evidence.

Case 1

A 70-year-old male patient sought the emergency room with a complaint of runny nose associated with dry cough for 5 days. One day ago he developed fever, mental confusion, lack of appetite and prostration. As a personal history, he reported arterial hypertension and epilepsy on carbamazepine. On physical examination, she was feverish, with an axillary temperature of 37.8°C, heart rate of 110bpm, blood pressure of 140x80mm Hg, respiratory rate of 25 irpm and 83% saturation in room air. Lung auscultation revealed crackles on the left base.

Laboratory tests showed lymphopenia, increased C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer. Other examinations and laboratory progress are shown in Table 1. The admission chest radiography showed a discrete bilateral infiltrate (Figure 1). The diagnostic hypothesis of sepsis of pulmonary focus with influenza syndrome was made, and the possibility of infection by SARS-CoV-2 was



raised. Antibiotic therapy with Piperacillin-Tazobactam, azithromycin, and oseltamivir was started, viral panel and PCR collected for COVID-19 (which proved to be positive in 24 h) and the patient was referred to the ICU.

On the second day of admission to the ICU, the patient developed respiratory failure and decreased level of consciousness, being submitted to orotracheal intubation and initiation of invasive mechanical ventilation. The transthoracic echocardiogram showed no relevant changes, with preserved ejection fraction. Due to the clinical worsening, it was decided to start enteral hydroxychloroquine and to suspend other medications commonly associated with an increase in the QT interval, such as ondansetron, bromopride and haloperidol. The QTc interval was monitored from the first day of ICU admission with a daily electrocardiogram (ECG) as shown in Figure 2, which remained within the normal range until the sixth day of ICU. On the seventh day, the patient presented sinus bradycardia, enlargement of the QTc interval, and Q wave in D1 and in AVL, accompanied by hemodynamic worsening, with severe hypotension, hyperlactatemia, and metabolic acidosis. A new transthoracic echocardiogram was performed, which showed diffuse hypokinesia with a drop in ejection fraction to 30% and an increase in the levels of ultra-sensitive troponin I (1038ng / dL), with a reference value of up to 25ng / dL. Dobutamine was started in a progressively higher dose up to 15 mcg / Kg / min, with stabilization of the condition. There were no hydroelectrolytic disturbances. Hydroxychloroquine and azithromycin were suspended. On the ECG the following

day, the QT interval had normalized, with no further QT prolongation after medication was discontinued. Repeated echocardiogram with partial recovery of the left ventricular ejection fraction to 45%.

The patient evolved with multiple complications during hospitalization with acute renal failure requiring hemodialysis, epileptic seizures, and urinary tract infection, progressing to death on the 22nd day of hospitalization.

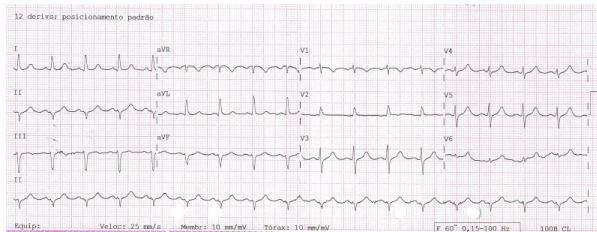
Case 2

Female patient, 92 years old, brought by her daughter to the emergency room with a history of dyspnea for 1 day, associated with generalized indisposition and weakness. She denied fever or flu-like symptoms. Daughter reported previous history of arterial hypertension, previous stroke with motor sequelae, lung cancer with radio surgery 6 years ago, and renal neoplasia with left nephrectomy 10 years ago, both without evidence of current disease.

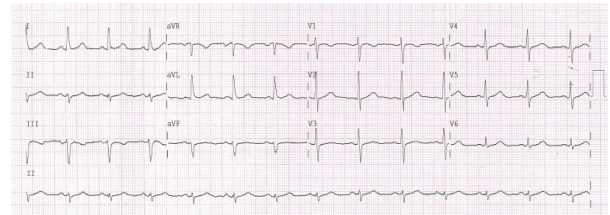
Physical examination revealed dyspnea, with blood pressure 208x102 mm Hg, heart rate 134 bpm, respiratory rate 25 irpm, saturating 75% in room air, with cyanosis of the extremities. Lung auscultation demonstrated diffuse bilateral crackles. Oxygen support was started with a reservoir mask at 10 L / min with good clinical response, as well as infused nitroglycerin and administered furosemide.

On admission examinations, patient with leukocytosis and relative lymphopenia, high CRP, in addition to increased D-dimer, troponin, and BNP. Other

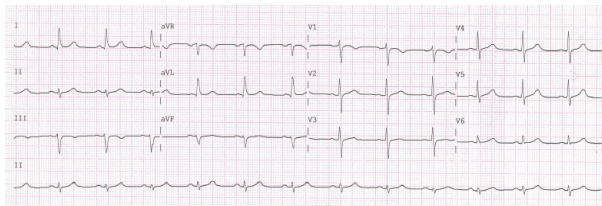
A – ECG at admission. HR 100bpm,
QT 360ms QTc 423ms



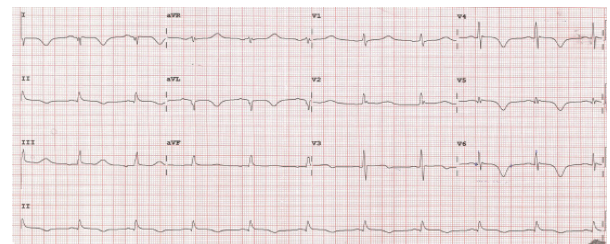
D – 6th day in the ICU. HR 107bpm,
QT 360ms, QTc 432ms



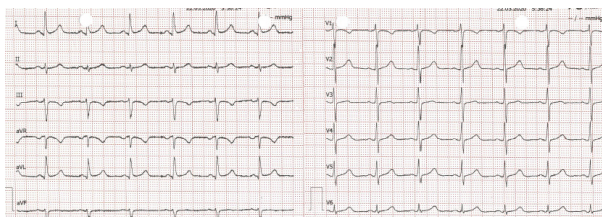
B – 2nd day in the ICU.
HR 75BPM QT 360ms QTc 391ms



E – 7th day in the ICU. HR 60bpm,
QT 580ms, QTc 603ms



C – 4th day in the ICU. HR 83bpm,
QT 360ms, QTc 340 ms



F – 8th day in the ICU. HR 100bpm,
QT 560ms, QTc 465ms

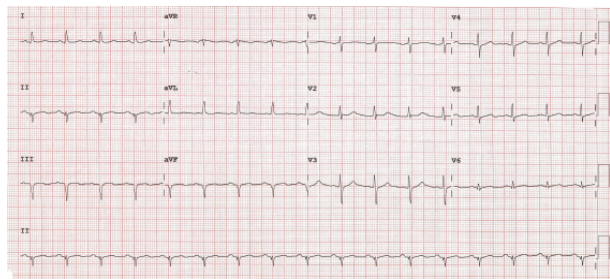


Figure 2 – Electrocardiographic evolution of the patient Case 1. A – Admission to the ICU, B – 2nd day in the ICU – day of prescription of chloroquine C – 4th day in the ICU, control of the onset of chloroquine; D – 6th day in the ICU; E – 7th day in the ICU – enlargement of the QTc interval (≈ 600 ms) and appearance of lateral inactive area, F – 8th day in the ICU – normalization of the interval. ECG: electrocardiogram; HR: heart rate; ICU: intensive care unit.

| Table 1 – Case 1 clinical and laboratory data | | | | | | | | | | |
|---|-----------|---------|----------|----------|---------|---------|---------|---------|----------|---------|
| | Admission | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D 10 |
| Hemoglobin (g/dL) | 14.8 | 13.1 | 13.4 | 12.7 | 13.2 | 13.5 | 14 | 14.1 | 13.8 | 8.9 |
| Hematocrit (%) | 45.4 | 38.6 | 41.4 | 38.5 | 40.2 | 41.3 | 42.2 | 42.9 | 41.1 | 28.2 |
| Leukogram (cells/mm ³) | 8050 | 9170 | 12610 | 8900 | 9730 | 14950 | 14010 | 17780 | 14080 | 37580 |
| Band cells (%) | 4% | 5% | 3% | 2% | 1% | 1% | 0 | 7% | 3% | 2% |
| Neutrophils (%) | 76% | 83% | 80% | 78% | 80% | 80% | 87% | 79% | 80% | 80% |
| Lymphocytes (cells/mm ³ - %) | 805-10% | 642-7% | 1261-10% | 1602-18% | 681-7% | 1047-7% | 981-7% | 1067-6% | 1408-10% | 12% |
| Platelet (cells/mm ³) | 233.000 | 204.000 | 243.000 | 244.000 | 290.000 | 327.000 | 340.000 | 280.000 | 341.000 | 261.000 |
| Urea (mg/dL) | 53 | 38 | | 37 | 53 | 67 | 107 | 63 | 61 | 131 |
| Creatinine (mg/dL) | 1.50 | 1.20 | 1.72 | 2.05 | 2.23 | 3.27 | 4.73 | 2.57 | 2.64 | 0.67 |
| Sodium (mEq/L) | 135 | 136 | 141 | 139 | 139 | 141 | 140 | 139 | 130 | 135 |
| Potassium (mEq/L) | 3.7 | 3.3 | 3.6 | 3.4 | 2.9 | 3.2 | 3.4 | 4.8 | 4.5 | 5.5 |
| Ionic calcium (mmol/L) | 1.08 | 1.01 | 1.15 | 0.97 | 0.96 | 0.95 | 0.97 | 0.96 | 1.09 | 0.97 |
| Phosphorus (mg/dL) | | 3.3 | 1.02 | | 4.5 | 4.2 | 3.6 | 4.5 | 2.5 | |
| Chlorine (mmol/L) | | 107 | | | 92 | 93 | 92 | 97 | 103 | 101 |
| Magnesium (mg/dL) | | 2.0 | 1.8 | | 1.6 | 1.7 | 2.0 | 1.9 | 1.4 | 1.6 |
| BNP (pg/mL) | | 18 | | 23 | 25 | 110 | 1120 | 1540 | 1000 | 154 |
| Troponin (mg/dL) | | >5 | >5 | >5 | >5 | >5 | 1038 | 115 | 192 | 109 |
| Ferritin (ng/mL) | | 631 | | | | 1137 | 1248 | 1755 | 1471 | 5095 |
| D-dimer (ng/ml) | 928 | 1200 | 1470 | 2035 | 2561 | | 6064 | 5163 | 4813 | 8322 |
| CRP (mg/dL) | 24.9 | 28.13 | 30.57 | 32.11 | 35.72 | 36.35 | 36.16 | 26.03 | 12.55 | 11.30 |
| Lactate (mg/dL) | 18 | 18 | 14 | 23 | 22 | 32 | 41 | 35 | 24 | 20 |
| LDH (UI/l) | | 448 | 576 | 499 | 526 | 533 | 539 | 439 | 237 | 543 |
| SWAB- COVID-19 | Positive | | | | | | | | | |
| Clinical Data | | | | | | | | | | |
| Use of vasopressors | | X | X | X | X | X | X | X | X | |
| Use of inotropic | | | | | | | | X | X | |
| Mechanical ventilation | | X | X | X | X | X | X | X | X | |
| LVEF (echocardiogram) | 64% | | | | | | 30% | | 45% | |
| Hemodialysis | | | | | | | X | | | X |

BNP: brain natriuretic peptide; PCR: C-reactive protein; LDH: lactate dehydrogenase; QTc: corrected QT interval; LVEF: left ventricular ejection fraction.

examinations and laboratory evolution are available in Table 2. Imaging tests showed bilateral infiltrate with irregular and peripheral distribution pattern on chest radiography and echocardiogram with preserved ejection fraction (61%), without segmental changes, with mild diastolic dysfunction (Figure 3).

Diagnostic hypotheses were made for acute hypertensive lung edema, associated with probable sepsis of pulmonary focus. Even without a typical clinical condition, due to the radiological pattern and the current pandemic context by COVID-19, it was decided to collect viral panel and CRP for SARS-Cov-2, in addition to starting empirical antibiotic therapy with ceftriaxone, azithromycin and oseltamivir. After reassessment, the ICU team decided to start chloroquine diphosphate on suspicion of COVID-19 (later confirmed).

Since then, other medications with the potential to prolong the QT interval were avoided and the patient was submitted to ECG daily - the QTc interval did not change in any routine ECG, as shown in Figure 4. On the second day of evolution, the patient presented increased troponin, without repercussions on ECG and ventricular function. On the fourth day of evolution, in the absence of clinical improvement, the antibiotic was switched to Piperacillin-Tazobactam. The next day, the patient developed acute respiratory failure, being submitted to orotracheal intubation and initiation of mechanical ventilation. After a few hours, she presented ventricular tachyarrhythmia with progression to cardiorespiratory arrest (CRA); electrocardiographic monitoring at the time of CRA demonstrated Torsades de Pointes

(Figure 4F). After cardiopulmonary resuscitation with defibrillation, the perfusion rate returned. The ECG after the event showed only right bundle branch block, which disappeared on a routine ECG the following day. The transthoracic echocardiogram after CRA maintained preserved EF (60%), without segmental deficit. After the event, the patient evolved with progressive clinical worsening due to multiple organ dysfunction, progressing to death on the 7th day of ICU stay.

In both cases presented, in addition to the combined use of chloroquine or hydroxychloroquine with azithromycin, patients were aging adults and were in the ICU in critical condition, which increases the chance of cardiovascular complications, both of ventricular dysfunction and ventricular arrhythmia. The first patient possibly had myocarditis (drop in ejection fraction, elevation of troponin and appearance of Q wave in DI and AVL), evolving with bradycardia and cardiogenic shock. The prolongation of the QT interval results from the combination of chloroquine and azithromycin, facilitated by bradycardia and myocardial injury. Myocardial inflammation alters the membrane's action potential and the inflammatory mediators, including cytokines, and potentiate the blocking of hERG channels, predisposing to Torsades de Pointes.

In the second case, the patient had a sudden evolution to Torsades de Pointes, without documentation of the prolongation of the QT interval, which may have punctually preceded the arrhythmic event. The presence of atrial bigeminy eventually contributed to the dispersion of repolarization due to the irregularity of the

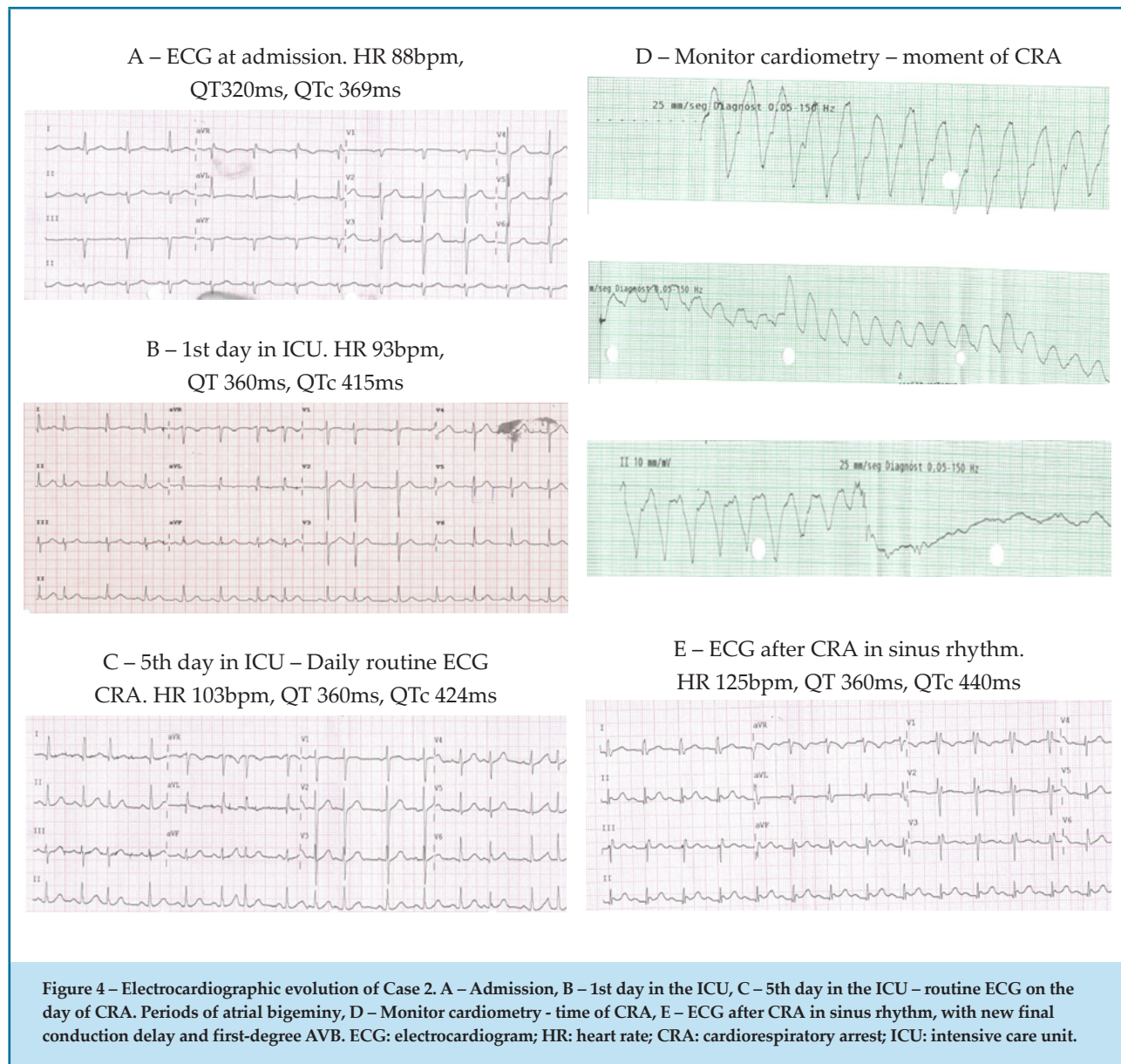
A – Admission to the ICU



B – First day of admission



Figure 3 – Radiographic evolution of Case 2. A – Admission to the ICU, B – 1st day of hospital admission. ICU, intensive care unit.



RR interval. There were also a PR prolongation, a new final conduction delay, observed after CRA, in addition to early inferior repolarization, demonstrating the transmural dispersion in the plateau phase of the action potential, which may have potentiated arrhythmogenesis or be just an electrical phenomenon after CRA.

This will probably be the reality for most of the patients in whom these drugs will be administered for the treatment of severe COVID-19 infection - they will often be older adults, hemodynamically unstable using one or more vasopressors and on mechanical ventilation, with delicate handling of volume, often resulting in electrolyte disturbances.

If the option is to use these medications, it is necessary to use tools to identify the subgroup of individuals who, either by genetic predisposition (such as Long QT syndrome, with an incidence of 1:2000) or by the presence of multiple modifiable and non-modifiable factors for long acquired QT, have a greater risk for exposure to drugs that prolong QT. A risk score validated by Tisdale and colleagues to predict QT prolongation in hospitalized patients can be used for this purpose.²³ The Tisdale score ≤ 6 indicates low risk, 7-10 moderate risk, and ≥ 11 high risk of prolonged QT related to drug use (Chart 1).

Therefore, the position at the moment is to employ the association of chloroquine / hydroxychloroquine with

Table 2 – Clinical-laboratorial data Case 2.

| | Admission | D1 | D2 | D3 | D4 | D5 | D6 |
|---|-----------|---------|----------|----------|---------|----------|----------|
| Hemoglobin (g/dL) | 11.5 | 11.2 | 10.1 | 10.5 | 13.3 | 10.3 | 10.4 |
| Hematocrit (%) | 34.1 | 33.1 | 30.1 | 32.6 | 39.4 | 29.2 | 30.9 |
| Leukogram (cells/mm ³) | 15990 | 9850 | 11800 | 10830 | 5290 | 9300 | 16980 |
| Band cells (%) | 0 | 0 | 0 | 0 | 3% | 3% | 0 |
| Neutrophils (%) | 54% | 80% | 87% | 70% | 74% | 77% | 84% |
| Lymphocytes (cells/mm ³ - %) | 1339-8.5% | 985-10% | 1298-11% | 1083-10% | 952-18% | 1023-11% | 2038-12% |
| Platelets (cells/mm ³) | 249.000 | 204.000 | 198.000 | 240.000 | 166.000 | 272.000 | 298.000 |
| Urea (mg/dL) | 43 | 47 | 53 | 59 | 52 | 49 | 37 |
| Creatinine (mg/dL) | 1.13 | 1.04 | 1.48 | 1.37 | 1.27 | 1.09 | 0.80 |
| Sodium (mEq/L) | 129 | 131 | 134 | 139 | 137 | 139 | 135 |
| Potassium (mEq/L) | 4.2 | 3.0 | 3.0 | 3.2 | 2.9 | 3.5 | 3.6 |
| Ionic calcium (mmol/L) | | 1.05 | 1.18 | 1.18 | 1.14 | 1.13 | 1.41 |
| Phosphorus (mg/dL) | | | 4.1 | 3.8 | | 3.8 | |
| Chlorine (mmol/L) | | | | | | 92 | |
| Magnesium (mg/dL) | | 1.5 | 2.4 | 1.7 | 1.5 | 1.6 | 2.1 |
| BNP (pg/mL) | 1220 | | 916 | | 483 | 309 | 347 |
| Troponin (mg/dL) | 55 | 224 | 109 | 40 | 35 | 25 | 490 |
| Ferritin (ng/mL) | | 807 | 554 | 640 | 772 | 761 | 2653 |
| D-dimer (ng/ml) | 2054 | | 1418 | | | | |
| CRP (mg/dL) | | 8.16 | 15.27 | 17.76 | 16.27 | 13.92 | 1.27 |
| Lactate (mg/dL) | 23 | 14 | 8 | 8 | 14 | 10 | 119 |
| LDH (UI/l) | | 416 | 397 | 440 | 447 | 545 | 143 |
| SWAB-COVID-19 | Positive | | | | | | |

Clinical Data

| | | | | | | | |
|------------------------------------|--|-----|--|--|--|---|-----|
| Use of vasopressors | | | | | | X | X |
| Use of inotropic | | | | | | X | X |
| Mechanical ventilation | | | | | | X | X |
| Ejection Fraction (echocardiogram) | | 61% | | | | | 60% |

BNP: brain natriuretic peptide; CRP: C-reactive protein; LDH: lactate dehydrogenase; QTc: corrected QT interval; LVEF: left ventricular ejection fraction.

azithromycin with caution in patients with heart disease, and minimize the use of expendable drugs that prolong the QT interval directly (potassium channel blockers) or indirectly (by drug interaction). Electrocardiographic monitoring should be strengthened in patients who develop myocardial injury or cardiac arrhythmias.

Author Contributions

Conception and design of the research: Crivelari NC, Hajjar LA. Acquisition of data: Souza AC, Hajjar LA. Writing of the manuscript: Crivelari NC, Oliveira GQ, Park CHL, Riemma GC, Costa IBSS. Critical revision of the manuscript for intellectual content : Lacerda MVG, Oliveira GMM, Darrieux F, Sacilotto L, Hajjar LA.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Hospital Pró-Cardíaco* under the protocol number CAAE: 3348.4020.8.0000.5533. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

| Tisdale risk score | |
|-------------------------------|-----------|
| Risk factors | Points |
| Age ≥ 68 years | 1 |
| Female sex | 1 |
| Loop diuretic | 1 |
| Serum K + ≤ 3.5 mEq / L | 2 |
| ECG admission with QTc ≥450ms | 2 |
| Acute Myocardial Infarction) | 2 |
| ≥ 2 drugs that prolong QTc | 3 |
| Sepsis | 3 |
| Cardiac insufficiency | 3 |
| A drug that prolongs QTc | 3 |
| Maximum risk score | 21 |

Chart 1- Tisdale risk score for the prediction of QT prolongation in hospitalized patients.

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