

## REVIEW ARTICLE

## Cardiac Arrhythmias and Covid-19

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### Abstract

Cardiovascular manifestations of COVID-19 include cardiac rhythm disturbances, whose mechanisms, incidence, and most common types are not well established in this population. Intense inflammatory response and metabolic activity contribute to recurrence of pre-existing arrhythmias, and other arrhythmias can occur due to myocardial injury, acute coronary insufficiency, and electrolyte disturbances. Brady- and tachyarrhythmias, as well as conduction disorders have been described. QT interval prolongation and fatal ventricular arrhythmias (*Torsades de Pointes*) may result from the pathological process or adverse effect of drugs (antiarrhythmics, chloroquine / hydroxychloroquine, azithromycin and antivirals). Patients with congenital heart disease and hemodynamic repercussions, patients with signs of heart failure, pulmonary hypertension, cyanosis, hypoxemia, and those who underwent heart transplantation and immunosuppression are at greater risk. In patients with implantable cardioverter-defibrillators (ICDs), the risk depends on the presence of structural heart disease. In the course of COVID-19, in-person assessment of these patients should be limited to high-risk situations, including syncope, worsening of heart failure and shock delivery by ICDs. Likewise,

### Keywords

Coronavirus Infections; Cardiac Arrhythmias; Artificial Pacemaker.

cardiac implantable electronic device implantation or replacement surgery should be limited to emergency and urgent cases, including symptomatic high-degree atrioventricular block, ICD for secondary prevention and pulse generator replacement due to battery drain.

### Introduction

The infection by SARS-CoV-2, the virus that causes COVID-19, may lead to clinical manifestations that directly affect several organs and systems. Although the COVID-19 is a primarily respiratory disease, many studies have suggested a cardiovascular involvement, especially in the group of patients who require hospitalization.<sup>1,2</sup> Clinical presentation and cardiac involvement may vary from asymptomatic disease to development of myocardial disease, hemodynamic instability, and rhythm disturbances.

Regarding cardiac arrhythmias, the real incidence, and the more common types of arrhythmias in SARS-CoV-2 infection is still unknown. So far, due to limited information on cardiac electrical disturbances related to COVID-19, current recommendations on the management of arrhythmias during the infection are based on existing evidence before the pandemic.

The current review aims to explore the pathophysiological mechanisms involved in arrhythmogenic cardiomyopathy, as well as clinical and therapeutic features of adult and pediatric COVID-19 patients, and patients with implantable cardiac electronic devices.

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### Pathophysiology

Elevation of troponin in up to 30% of patients in the early stages of COVID-19 is an indication for cardiac stress and injury. Increased levels of brain natriuretic peptide (BNP) levels have been reported in similar proportions.

Cardiovascular damage induced by COVID-19 has not been fully elucidated, and several mechanisms have been proposed:

- a) Intense systemic inflammatory response, with increased cytokine levels (particularly interleukin 6, IL6), which may lead to injury of multiple organs, including myocardial cells;
- b) Myocardial injury resulting from an imbalance between an increased cardiometabolic demand and reduced oxygen supply due to significant hypoxemia induced by severe pneumonia; myocarditis, microvascular injury and stress-related cardiomyopathy may also be involved in the development of myocardial injury;
- c) Acute coronary syndrome caused by atherosclerotic plaque rupture. Plaque instability and rupture

may be caused by viral infection and consequent systemic inflammatory response, culminating in acute myocardial infarction. Likewise, dysregulation of the renin-angiotensin-aldosterone system may predispose to plaque rupture. Type 2 infarction is observed in some patients, as a result of hypoxemia induced by an increased oxygen demand by the myocardium and hypotension.<sup>3,4</sup>

Based on current knowledge, cardiac arrhythmias in COVID-19 patients seem to be caused by multiple factors from intense inflammation and metabolic activity, which favor the recurrence of arrhythmias, until the emergence of new arrhythmias induced by myocardial injury and acute coronary failure. IL-6, TNF $\alpha$  and IL-1 have been found to prolong the ventricular action potential duration, modulating the expression and/or function of cardiomyocyte ion channels, specifically potassium and calcium channels (inflammatory cardiac channelopathies).<sup>5</sup>

In addition to direct cardiac effects, systemic inflammation can also predispose to QT interval

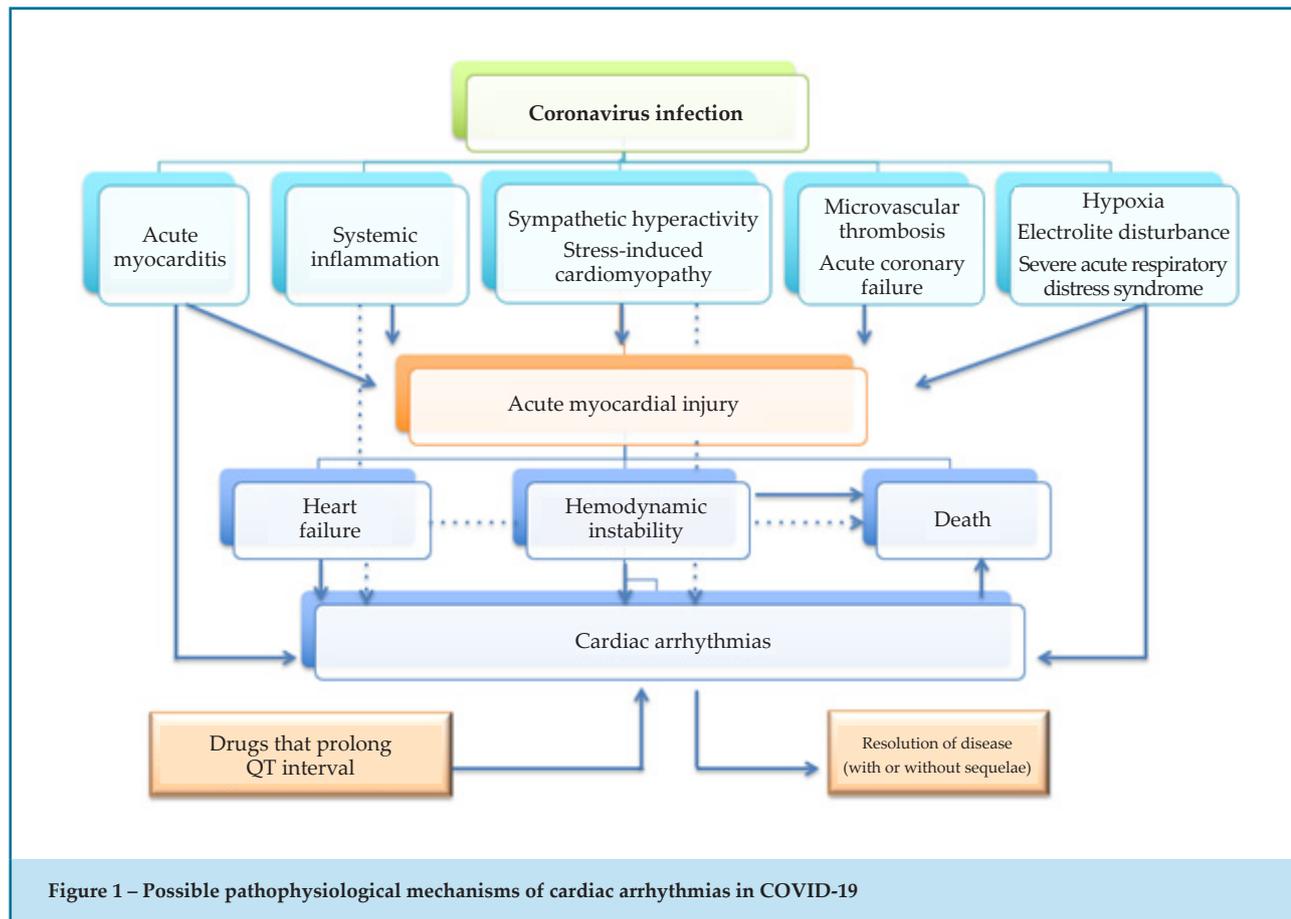


Figure 1 – Possible pathophysiological mechanisms of cardiac arrhythmias in COVID-19

prolongation and consequently polymorphic ventricular tachycardia – *Torsades de Pointes* (TdP). Inflammatory cytokines can cause hyperactivation of cardiac sympathetic nervous system, mediated by hypothalamus (inflammatory reflex), and of the peripheral system (with activation of left stellate ganglion). These processes are recognized as triggers to arrhythmic events and life threat in patients with long QT syndrome. In addition, IL-6 inhibits p450 cytochrome, mainly the CYP3A4, which enhances the bioavailability of several drugs, including those that prolong the QT interval.

Experimental studies in rats infected by SARS-Cov-2 have also demonstrated changes in cardiac conduction system secondary to myocarditis and ventricular dysfunction.<sup>6</sup> Bradycardia has also been reported in critically ill patients, as a result of increased vagal tone.<sup>7</sup> So far, there is no report on the direct involvement of the conduction system in COVID-19 in humans.

Electrolyte disturbances, direct effects of cytokines, and drugs that prolong the QT interval may favor the occurrence of arrhythmias, particularly high-risk arrhythmias such as TdP. Thus, the combined use of chloroquine with azithromycin, associated with predisposing factors such as ventricular dysfunction, concomitant use of antiarrhythmic drugs (e.g. magnesium and potassium deficiency), older age, among others, can contribute to the development of polymorphic ventricular tachycardias (TdP). In a retrospective study, Wang et al. showed that 23 (16.7%) of 138 hospitalized patients with COVID-19 developed some form of arrhythmia. The incidence of arrhythmia was higher in more severely ill patients, treated in the intensive care unit (44% vs. 6.9%). The authors did not specify the types of arrhythmia detected.<sup>2</sup>

These factors, either alone or together, may culminate in the emergence of atrial and ventricular tachyarrhythmias; the involvement of the cardiac excito-conductor system, combined with sinus bradycardia, atrioventricular, interventricular, and intraventricular block may also occur.

### Bradyarrhythmias

Bradyarrhythmias are common in many clinical scenarios, varying from structural defects of cardiac conduction system, physiological adaptations to transient mechanisms (vagal modulation, pharmacological effects, ischemia, inflammatory activity) to pathological conditions.

Patients with previous structural heart disease are at higher risk for complications of COVID-19, with potentially fatal outcome. Many of these patients have a history of bradycardia or of use of medications with negative chronotropic effect. The use of beta-blockers, dihydropyridine calcium channel blockers, amiodarone, digoxin, among others, is common among hypertensive patients with heart failure or coronary artery disease. Also, an exacerbated inflammatory response, with myocardial involvement, may cause bradyarrhythmias with potential hemodynamic instability, even transient ones.

In general, sinus bradycardia, junctional rhythm, first- and second-degree atrioventricular block (Mobitz I, with a narrow QRS complex), are related to reflex and adaptative mechanisms, or to structural disease at the atrioventricular node level, above the bundle of His. These changes seem to have better prognosis and better response to vasoactive agents and atropine and are usually transient. Advanced or third-degree atrioventricular block reflects a more severe involvement of the infra-Hisian conduction and usually requires artificial cardiac stimulation, even temporarily.

Therefore, COVID-19 patients with bradyarrhythmias may require special attention regarding the prevention of complications of systemic inflammatory response, worsening of arrhythmia by iatrogenic effect and eventual need of pacemaker (PM).

### Atrial fibrillation

The incidence of atrial fibrillation (AF) and atrial flutter (AFL) is unknown in patients with COVID-19.<sup>30</sup> Based on previous studies, it is known that, in critically ill patients with SARS or septicemia, AF is not uncommon and is associated with higher mortality rates.<sup>8,9,10</sup>

Similar to patients without COVID-19, the treatment of AF and AFL should be based on the control of ventricular response and heart rhythm, and prevention of thromboembolic events.

Electrical cardioversion (ECV) is indicated for patients with hemodynamic instability. In the context of COVID-19, it is important to highlight the need for protecting health care workers involved in this procedure, especially in cases of orotracheal intubation due to the high risk of aerosol contamination.<sup>11</sup>

Amiodarone is the drug of choice for COVID-19 patients, either for reversion of stable AF or to avoid recurrence after ECV. It is important to identify and correct factors that can increase the risk for proarrhythmic

effects, such as electrolyte disturbance, and concomitant use of drugs that increase QT interval. Despite the absence of robust scientific evidence on their efficacy in the treatment of COVID-19, the combination of hydroxychloroquine with azithromycin has been used in these patients. However, it is worth to mention that these medications can cause QT interval prolongation, which could, in theory, exacerbate the effect.<sup>12,13</sup> Also, other drugs previously tested and currently used against the SARS-CoV-2 infection, may also affect the QT interval and lead to more severe arrhythmias like the TdP. An updated list of drugs that cause QTc prolongation is available at online databases (e.g. the CredibleMeds® - <https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf>).

It is of note that the more severe forms of SARS-CoV-2 infection could, in theory, contribute to the development and persistence of AF. In addition, maintenance of sinus rhythm may be challenging in the presence of acute respiratory failure, severe inflammation, metabolic and electrolyte disturbances, as well as increased sympathetic tone activation. In this critical scenario, the choice for the primary control of heart rate without ECV attempts for atrial fibrillation until stabilization of patient's clinical status should be considered.<sup>13</sup>

As above mentioned, attention should be paid to interactions of drugs that increase the risk of QT interval prolongation and the occurrence of potentially fatal arrhythmias. In this regard, it is crucial to assess the degree of risk/benefit of continuing or temporarily discontinuing antiarrhythmic drugs during the acute phase of COVID-19. For example, hemodynamically stable patients with AF, receiving antiviral treatment, discontinuation of antiarrhythmic agents should be considered to prevent the risk of proarrhythmic effects. In this case, the use of beta-blockers (if not contraindicated) may be a good alternative for the control of ventricular rate.

Finally, electrocardiographic monitoring of QT interval and electrolyte disturbances (especially potassium and magnesium) should be conducted with appropriate corrections before and after the use of drugs that prolong QT interval is initiated.

Anticoagulation is indicated to both valvular AF (patients with metallic prosthetic valves or moderate/severe mitral stenosis) and non-valvular AF. In the latter, anticoagulation has been advocated for patients with CHA<sub>2</sub>DS<sub>2</sub>VASC  $\geq 2$  for men and  $\geq 3$  for women. In hemodynamically stable patients with nonvalvular AF and no mechanical ventilatory support, direct oral

anticoagulants are the drugs of choice, whereas for patients with valvular AF, warfarin is indicated. Possible drug interactions that could affect both the efficacy of anticoagulants and the risk of bleeding complications (e.g. antiviral drugs and direct anticoagulants) should be evaluated.

Subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin molecular should be preferred for hemodynamically unstable patients and those on ventilatory support with orotracheal intubation.

As previously mentioned, these recommendations have been developed on the basis of accumulated knowledge before the COVID-19 pandemic. Thus, a better understanding of the pathophysiology of COVID-19 should, in near future, help in the management of these patients including on the choice of prophylactic anticoagulation for prevention of thromboembolic events in AF and AFL. Critically-ill patients with COVID-19 are at higher risk for thrombotic complications, which is particularly important in AF.

Due to the lack of controlled randomized clinical trial that would help in defining the best therapeutic approaches in each clinical situation, a systematic prevention of thromboembolic phenomena should be implemented. It is worth pointing out that computed tomography has been shown as an effective alternative to echocardiography for detection of thrombus in the left atrium. Such strategy may be valuable for COVID-19 patients, to mitigate the risk of upper airway contamination.<sup>14</sup>

### Ventricular tachycardia and ventricular fibrillation

The incidence of malignant ventricular arrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF) in COVID-19 is still unknown. The risk of VT and VF is believed to be higher in more severely ill patients, reflected by the higher intensity of metabolic derangement, hypoxemia, neurohumoral and inflammatory stress, and greater myocardial injury. Besides, due to infection, these conditions may be even more complicated in patients with previous cardiovascular disease or ventricular arrhythmias.<sup>30</sup>

A recent study showed a 5.9% incidence of VT or VF in patients hospitalized for COVID-19, with higher frequency in those with elevated troponin.<sup>15</sup> In fact, increased troponin levels seem to be a marker of severity of COVID-19 and are associated with hemodynamic instability and cardiac arrhythmias.

While hemodynamically unstable patients with VT or VF should be submitted to ECV or defibrillation, for patients with polymorphic VT and QT interval prolongation (TdP), other strategies including intravenous administration of lidocaine and/or magnesium sulfate, elevation of heart rate with isoproterenol administration (except patients with long-QT syndrome), PM implantation, in addition to discontinuation of negative inotropic agents and drugs that prolong QT interval, and maintenance of serum potassium levels  $>4.5$  mEq/L must be considered.

For patients with sustained monomorphic VT, without hemodynamic instability, ECV (particularly intubated patients and those on artificial ventilation); intravenous lidocaine (especially patients with prolonged QT interval and/or use of drugs that prolong the QT interval), and intravenous amiodarone (for those with structural heart disease and ventricular dysfunction) should be considered. Amiodarone should be avoided in patients with prolonged QT interval or those using drugs that prolong the QT interval.

### Electrical storm

Electrical storm is defined as three or more episodes of sustained VT or VF within 24 hours. It is a serious condition with high mortality rates. Electrical storm is more commonly seen in patients with structural heart disease, and the main predictive factors include severity of ventricular dysfunction, older age and previous VT or VF.<sup>16</sup>

When an electrical storm occurs, in addition to the above-mentioned therapeutic strategies for VT/VF, the use of intravenous lidocaine and beta-blockers (Esmolol) must be considered for patients in whom amiodarone therapy was unsuccessful or its use is contraindicated. Deep sedation with orotracheal intubation and artificial ventilatory support (again highlighting the importance of protecting the health care workers from the risk of aerosol transmission), and transient PM aiming at reversing the arrhythmia by rapid ventricular stimulation and acting as an adjuvant to pharmacological therapy should also be useful.

### Children and congenital heart diseases

Severe SARS-CoV-2 infection has been rarely found in children, who have usually presented a milder form of the disease, with better prognosis. So far, risk of

vertical transmission by SARS-CoV-2 is probably very low, compared with adults.<sup>6, 17, 18, 19</sup>

The largest study involving children with COVID-19 included 2,143 patients. Most of them (94.1%) were asymptomatic, or had mild or moderate symptoms and, for this reason, the actual infection rate is believed to be much higher.<sup>20</sup>

Recent data have suggested that asymptomatic or oligosymptomatic individuals have potentially infectious particles of SARS-CoV-2 in nasopharyngeal secretions, which favors the transmission to close contacts. Another important finding in COVID-19 transmission was the detection of the virus in fecal samples from asymptomatic children, with longer virus shedding period compared to the upper respiratory samples, suggesting a prolonged fecal-oral transmissibility for COVID-19.<sup>20</sup> The presence of SARS-CoV-2 for a long period in nasal secretion and feces from infants and children has important implications for dissemination of the virus in nurseries and schools, and even at home. Consequently, infants and children may play an important role in community transmission of COVID-19.

Individuals younger than 18 years old represent less than 2% of severely infected patients.<sup>17</sup> The reason why children are less likely than adults to be infected and harmed by SARS-CoV-2 has not been elucidated yet. Two hypotheses have been proposed to this fact: first, children, especially younger ones, would have higher immunity against the SARS-CoV2 virus due to repetitive exposure to different viruses, and second, the lower presence of angiotensin-converting enzyme 2, which has a high affinity for the viral protein.

The main symptoms found in children with COVID-19 are fever, dry cough, and fatigue. Few children have upper respiratory symptoms including nasal congestion and runny nose, and some patients also have gastrointestinal symptoms, including abdominal pain and discomfort, nausea, vomiting and diarrhea. Chest X-ray findings in these patients are normal or reveal unspecified pulmonary changes, with unilateral or bilateral lesions. Most children have normal chest computed tomography (CT) scans. Abnormal findings observed in critically ill adult patients, including lung consolidation, pleural effusion and enlarged lymph nodes, have been rarely found in children with COVID-19.<sup>18</sup>

Laboratory test results in the initial phase of COVID-19 show normal or low white cell count, with low lymphocyte count. Levels of hepatic and muscle enzymes, and myoglobin are elevated in some patients.

In moderately ill patients, elevation of C-reactive protein and erythrocyte sedimentation rate and normal procalcitonin is seen in most of them. Severely ill patients have increased d-dimer levels and low lymphocyte count. Complete blood count, urine and stool tests, coagulation test, biochemical tests, and identification of biomarkers of infection were performed in children with SARS-CoV-2 infection, with normal results in almost all of them. Few children, in contrast to adult patients, had leukopenia, leukocytosis, lymphopenia, or elevated transaminases.<sup>18</sup>

In the largest study on the severity of COVID-19 in children, Dong et al. reported that the infants were more vulnerable to severe SARS-CoV-2 infection (10.6% of all pediatric patients), and symptoms like pneumonia, central cyanosis (8.7% of the cases), and acute respiratory distress syndrome (ARDS), requiring mechanical ventilation (1.8% of the cases).<sup>21</sup> The proportion of severe and critical cases was 10.6 % in infants, 7.3% for the age group of 1-5 years, 4.3% for the age group of 6-15 years, and 2.8% for  $\geq 16$  years.

Children that are more susceptible to developing severe infection are those with developmental disabilities, children with congenital heart diseases, and other underlying diseases, including type 1 diabetes mellitus, cancer, and chronic pulmonary disease (e.g. asthma).

Of 345 children with confirmed COVID-19, the CDC (Centers for Disease Control and Prevention) reported that the most common underlying conditions were: chronic pulmonary disease (11.6%), cardiovascular disease (7.2%) and immunosuppressive conditions (2.9%).<sup>21</sup> The authors also reported an overall low mortality rate in children (0.18%) compared with adults (4.3%).<sup>6, 22</sup>

Despite the risk of contamination, breastfeeding should be encouraged since it is the best source of nutrients and antibodies, and so far, COVID-19 virus has not been detected in the breast milk. SARS-CoV-2-infected mothers should wash their hands frequently with soap and water or use alcohol-based hand sanitizer and wear a face mask. If a mother is too tired to breastfeed, milk should be expressed using a manual or an electric breast pump so that a healthy family member or caregiver may feed the infant.

According to the Brazilian Pediatric Society, COVID-19 patients with congenital heart disease and hemodynamic repercussion or manifestations of heart failure are more likely to have an unfavorable outcome. The clinical course tends to be benign in patients without hemodynamic

repercussion and patients in stable clinical conditions or no signs of cardiac decompensation after cardiac surgery or catheterization.

Children with unoperated congenital heart disease, significant hemodynamic repercussion (including signs of heart failure, pulmonary hypertension, cyanosis, and hypoxemia following) surgical correction of congenital heart defects, immunosuppressed children, and children submitted to cardiac transplantation are at increased risk for an unfavorable outcome in infectious diseases. Likewise, although specific data on pediatric patients with COVID-19 are still lacking, a strict social isolation is recommended for this population.<sup>23</sup>

Congenital heart disease patients considered at high risk of becoming seriously ill from COVID-19, according to the British Congenital Cardiac Association, are listed in Table 1.<sup>24</sup>

Similar to what has been observed in adults, the pathophysiology of COVID-19 in children may involve the development of cardiac arrhythmias due to intense inflammation and, eventually, myocarditis. Studies have suggested that inflammation is an important risk factor for long QT syndrome and TdP, mainly by direct electrophysiological effects of cytokines in the myocardium.<sup>6</sup> Also, changes in ventricular repolarization and QT interval prolongation, and consequent risk of proarrhythmia, may be caused by drugs like antiarrhythmic agents, azithromycin, hydroxychloroquine or chloroquine, and antivirals.<sup>18</sup>

The incidence of cardiac arrhythmias is not well established in SARS-Cov-2-infected children. Arrhythmias may occur due to primary diseases, individual or familial genetic disorders, or secondary to toxic and metabolic disorders, drug effects or current heart disease.

During an infection, several factors can trigger arrhythmias, which can be of difficult control. Clinical history and examination are essential for adequate diagnosis and management. Electrocardiographic monitoring of arrhythmia, especially by 12-lead electrocardiogram, can reduce the need for complementary tests. Correction of electrolyte disturbances should be the first step, combined with improvement of metabolic conditions, particularly hypoxia and anxiety

A careful pharmacological approach of arrhythmia should be performed due to the risk of proarrhythmia.<sup>18</sup> In this regard, a multidisciplinary team is needed and, in special situations, an arrhythmia specialist should be consulted.

**Table 1 – Congenital heart conditions associated with high risk of unfavorable outcome in COVID-19**

Single ventricle; Fontan circulation (total cavopulmonary connection)
Infants younger than one year with congenital heart disease, who require surgical repair or catheterization (e.g. interventricular communication, atrioventricular septal defect, Fallot tetralogy)
Chronic cyanosis (oxygen saturation persistently <85%)
Severe cardiomyopathies that require drug therapy
Congenital heart disease and use of medications to improve cardiac function
Pulmonary hypertension that requires drug therapy
Patients undergoing cardiac transplantation
Congenital heart disease and comorbidities like chronic renal disease and chronic pulmonary disease
<a href="https://www.bcca-uk.org/documents/my_files/COVID_BCCA_Vulnerable_groups_FINAL-18_March_2020.pdf">https://www.bcca-uk.org/documents/my_files/COVID_BCCA_Vulnerable_groups_FINAL-18_March_2020.pdf</a>

### Patients with cardiac implantable electronic devices (CIEDs)

*Pacemakers (PM), implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT).*

The use of CIEDs *per se* does not imply an increased risk of unfavorable outcome in COVID-19. This risk depends essentially on the presence of structural heart disease.<sup>13</sup> In PM patients with neurally mediated syncope, for example, the prevalence of structural heart disease is low. On the other hand, in patients undergoing CRT, the presence of dilated cardiomyopathy and reduced left ventricular ejection fraction is a prerequisite for PM implantation and put them at high risk. In patients with ICDs, there are two possible scenarios: (1) patients with structural (anatomical) heart disease and (2) ultrastructural changes (electrical, mainly channelopathies). Although the prevalence of severe outcomes is higher in the first group, special considerations should be made for channelopathies.<sup>5</sup>

### Patients with CIEDs and suspected or confirmed COVID-19

The real incidence and the types of cardiac arrhythmias that may be related to COVID-19 are not known.<sup>13</sup> A study<sup>2</sup> has reported a prevalence of 16.7%, 7% in ward patients and 44% in ICU patients

The pathophysiology of arrhythmias is complex and multifactorial. Due to few available data on the management of arrhythmias and ICDs in the context of the COVID-19 pandemic, consensus based on limited

information and on treatment of arrhythmias associated with other conditions has been used. New information may become available at any time, since attention of all medical societies is turned to this infection.

The general principles of the management of patients with CIEDs during the pandemic are directed towards managing financial resources to provide adequate treatment of all patients with COVID-19, minimize the risk of in-hospital infection among noninfected patients and health care workers, and continue to provide high-quality emergency care for CIED patients with life-threatening arrhythmias.<sup>13</sup>

### Cardiac arrhythmias in COVID-19 patients with CIED may occur in three situations:

1. Exacerbation of previous arrhythmias: in this case, the treatment of underlying disease and the use of antiarrhythmic agents are essential;
2. Arrhythmias caused by QT interval prolongation (TdP): in this case, it is recommended to correct electrolyte disturbances and hypoxemia; discontinue nonessential medications, evaluate the risk/benefit of the use of drugs that prolong the QT interval (such as chloroquine and azithromycin), and elevate heart rate (temporary PM insertion or reprogramming of permanent pacemaker by telemetry);
3. Development of new arrhythmias: after correction of systemic and metabolic causes, the presence of myocarditis, systemic inflammation, and myocardial ischemia should be considered.

The routine evaluation of patients with CIEDs should be postponed. In-person visits should be limited to patients with new symptoms (such as syncope, worsening of heart failure in patients on CRT, inappropriate shock delivery by ICDs), tonal or vibration alerts, suspicious of broken electrode, battery depletion, and abnormal heart rhythm (ICU, ward or remote monitoring).

Local protocols are recommended for the use of unique, dedicated programmers, with proper storage in designated areas, thorough cleaning before and after each use, and single-use personal protective equipment. Patient interview should be preferable performed via wireless communication technology, thereby avoiding person-to-person contact.

Invasive procedures using CIED should also be avoided until the infection is controlled and the patient shows clinical improvement.

### Pacemakers

Although there are no reports on PM failure in COVID-19, possible situations of PM malfunction are listed in Table 2.

### Implantable cardioverter defibrillators

Although there are no consistent data on the incidence of ventricular arrhythmias in COVID-19 patients, one center retrospectively reported an incidence of 5.9% of sustained VT and VF in hospitalized patients.

Myocardial injury, diagnosed by elevation of Troponin I, was more prevalent in the subgroup of patients with malignant arrhythmias (17.3%) compared with the subgroup without malignant arrhythmias (1.5%).<sup>29</sup> This finding suggests that the development of new malignant ventricular arrhythmias is a marker of myocardial injury and indicates the need for antiviral treatment and a more aggressive immunosuppressive therapy. Patients receiving ICD for secondary prophylaxis may experience exacerbation of VT/VF episodes precipitated by COVID-19. In addition, despite the absence of data on patients with COVID-19, correlations between seasonal influenza activity with the incidence of ventricular arrhythmias requiring therapy in patients with an ICD has been reported.<sup>29</sup> Based on the therapies delivered by the ICD, some situations may occur, and its differentiation may require electronic assessment (Table 3).

### Cardiac resynchronization therapy (CRT)

There are no reports on failure of CRT or on the outcome of CRT patients in COVID-19. However, due to reduced LVEF, there is a greater risk of severe outcomes. Considering the worsening of LVEF during the course of disease, an electronic evaluation of CRT is needed. Besides, continuous electrocardiographic monitoring of multiple channels and its comparison with telemetry data is useful. Finally, programming of CRT by transthoracic echocardiography may be useful in nonresponders.

**Table 2 – Possible pacemaker malfunction related to Covid-19.**

<b>Increased atrial stimulation rate</b>	Relative bradycardia, similar to what has been reported in typhoid fever. <sup>12</sup> Prone ventilation may also cause a fall in heart rate. <sup>26, 12</sup>
<b>Increased ventricular stimulation rate</b>	In animal experiments, the coronavirus infection caused second-degree atrioventricular block (AVB), secondary to myocarditis and heart failure. <sup>7</sup> Some drugs used in the treatment of COVID-19 (e.g, chloroquine) may cause distal AVB. <sup>7</sup>
<b>Increased stimulation threshold and loss of capture</b>	Caused by electrolyte disturbances, hypoglycemia, hypoxemia, drugs, myocarditis, and inflammatory state. Electronic programming is required.
<b>AHRE (Atrial High Rate Episodes)</b>	Atrial arrhythmias, combined with hypercoagulability may increase the incidence of thromboembolic events. In addition to the CHADS <sub>2</sub> VASC <sub>2</sub> score, a SIC (Sepsis-Induced Coagulopathy score) $\geq 4$ and elevation of d-dimer (more than five times the normal level or $> 3\mu\text{g}/\text{mL}$ ) <sup>28</sup> should be used to determine the initiation of anticoagulation.
<b>Need for reprogramming of the stimulation rate</b>	Due to inflammatory state and/or TdP, an elevation of heart rate may be needed to meet the metabolic demand and inhibit the formation of ectopic foci. Stimulation rates of 90 - 110ppm are usually applied. Eventually, the magnet mode is turned on with application of a magnet over the pulse generator, which, in most PMs, leads to a stimulation frequency of 90-110ppm and may be an useful strategy when the electronic programming is not available.

## Patients with CIEDs without suspected or confirmed Covid-19

### Routine assessment

Whenever possible, remote monitoring of patients with CIED should be preferred during the COVID-19 pandemic. When the remote evaluation is not possible, in-person visits are recommended in the following situations:

- New symptoms (syncope, worsening of heart failure in CRT patients, and shock delivery by ICD);
- Tonal or vibration alerts;
- Suspicious of broken electrode;
- Battery depletion (based on last evaluation)
- Abnormal heart rhythm (ICU, ward or remote monitoring).

### Invasive procedures

All patients should be considered potentially infected, and hence adequate protection and cleaning measures should be applied. Only in rare cases of patient and physicians with two consecutive negative PCR results within 48 hours, the facility is classified as free of COVID-19, and level A protection and cleaning measures should be routinely applied.<sup>13</sup>

Surgical procedures can be classified as urgent, semi-urgent and elective, according to the severity of the condition and time to surgery (Table 4).

### Final Considerations

The SARS-CoV-2 infection can cause cardiovascular changes that culminate in arrhythmias or worse outcomes of patients with previous heart disease. There is a wide variety of cardiac rhythm disturbances, and their presence does not necessarily imply a worse prognosis for SARS-CoV-2-infected patients. Underlying cardiac disease, *i.e.* cardiac “health”, is the main factor that influences cardiovascular outcomes. Likewise, there is no evidence that the presence of an electronic device *per se*, such as a PM or an ICD, is sufficient to influence the prognosis, without considering patient’s cardiac condition.

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**Table 3 – Possible effects of COVID-19 in patients with implantable cardioverter defibrillators**

<b>Inappropriate therapy</b>	Sinus tachycardia, atrial tachyarrhythmias, internal interference (disruption of the electrode cable) and external interference (myopotentials, electromagnetic interferences). In these cases, treatment of the causes is required.
<b>Sustained monomorphic ventricular tachycardia</b>	Commonly seen in patients with structural heart disease. The treatment aims to inhibit the arrhythmogenic activities with amiodarone, beta-blockers, lidocaine, procainamide, cervical ganglion infiltration, radiofrequency ablation.
<b>Polymorphic ventricular tachycardia in patients with channelopathies</b>	Triggers should be corrected. <i>Brugada syndrome</i> : control fever; <i>Congenital long QT syndrome</i> (cLQTS): optimize the dose of beta-blockers, switch off stimulation algorithms that may cause pacing pauses (hysteresis, intrinsic atrioventricular conduction search), drugs that prolong QT interval, correct thyroid dysfunction. Catecholaminergic polymorphic ventricular tachycardia (CPVT): beta-blockers, flecainide; sympathomimetics and adrenergics should be used with caution.
<b>Polymorphic ventricular tachycardia associated with QT prolongation (<i>Torsades de Pointes</i>)</b>	Multifactorial disease, mainly secondary to drug-drug interaction: discontinue nonessential drugs that prolong QT interval, correct ions and hypoxemia, evaluate risk/benefit of chloroquine/azithromycin, elevate the heart rate to 90-110 bpm (attention: in contrast to pacemakers, the application of a magnet on ICD pulse generators has no effect on magnetic heart rate and temporarily deactivates anti-tachycardia therapies).
<b>Polymorphic ventricular tachycardia associated with normal QT interval</b>	Usually secondary to myocardial ischemia or myocarditis. Specific imaging tests are useful.

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This article does not contain any studies with human participants or animals performed by any of the authors.

### Author contributions

Conception and design of the research: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Teixeira RA, Teixeira RA. Acquisition of data: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Borges VAG, Scanavacca MI, Martinelli Filho M, Teixeira RA. Analysis and interpretation of the data: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Borges VAG, Scanavacca MI, Martinelli Filho M, Teixeira RA. Writing of the manuscript: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Borges VAG, Scanavacca MI, Martinelli Filho M, Teixeira RA. Critical revision of the manuscript for intellectual content: Fagundes AA, Melo SL, Armaganijan LV, Kuniyoshi RR, Moraes LGB, Teixeira RA. Supervision / as the major investigator: Teixeira RA.

**Table 4 – Classification of surgical procedures in patients with implantable cardioverter defibrillators according to priority criteria**

<b>Urgent (days)</b>	<ul style="list-style-type: none"> <li>• Pacemaker implantation for symptomatic, high-degree atrioventricular block;</li> <li>• Pacemaker implantation for sinus node dysfunction with symptomatic pauses;</li> <li>• ICD implantation for secondary prophylaxis (recovered cardiac arrest or sustained ventricular tachycardia);               <ul style="list-style-type: none"> <li>• Replacement of pulse generators (PM/ICD) in dependent patient and in case of end-of-life battery;                   <ul style="list-style-type: none"> <li>• Electrode revision in symptomatic patients;</li> <li>• Extraction of the electrodes due to infection.</li> </ul> </li> </ul> </li> </ul>
<b>Semi-urgent (&lt; 3 months)</b>	<ul style="list-style-type: none"> <li>• Replacement of PM/ ICD/ CRT generator due to battery depletion detected by the elective replacement indicator (ERI);</li> <li>• ICD implantation for primary prophylaxis in high-risk patients;</li> <li>• PM implantation for sinus node dysfunction without pauses.</li> </ul>
<b>Elective (≥ 3 months)</b>	<ul style="list-style-type: none"> <li>• PM implantation for neurally mediated syncope;               <ul style="list-style-type: none"> <li>• ICD implantation for primary prophylaxis;                   <ul style="list-style-type: none"> <li>• CRT implantation;</li> <li>• Upgrade to ICD;</li> </ul> </li> <li>• Extraction of electrodes without infection;</li> <li>• Electrode revision in asymptomatic patients.</li> </ul> </li> </ul>

ICD: implantable cardioverter defibrillators; PM: pacemaker; CRT: cardiac resynchronization therapy

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