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Abstract
The coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) that first appeared in Wuhan, China. COVID-19 was found to have significant implications on the cardiovascular system. This is depicted by several manifestations such as myocardial injury, malignant arrhythmias, complicating the management of acute coronary syndrome, and even cardiogenic shock. Worse, the medications for COVID-19 had been known to induce cardiovascular side effects and had drug-drug interaction with anticoagulants. RAS blocker, as the holy grail of hypertension and heart failure medication, should also be continued despite COVID-19 infection.

Keywords: COVID-19, cardiovascular implications, medications

Introduction
Coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) that first appeared in Wuhan, China.1,2 SARS-CoV2 rapidly spread to almost every country in the world and COVID-19 was declared a pandemic by the World Health Organization on 11 March 2020.2 In Indonesia, COVID-19 has affected 11,192 confirmed patients with 1,871 patients recovered and 845 patients deceased (4 May 2020).3 A cohort study found that comorbidities present in COVID-19 patients include hypertension (30%), diabetes (19%), coronary heart disease (8%), chronic obstructive lung disease (3%), carcinoma (1%), and chronic kidney disease (1%).4 While in a large study of 44672 COVID-19 patients also in China, those with cardiovascular disease comprised 22.7% of all fatal cases.2 Another study in 138 hospitalized COVID-19 patients found that the most common causes of admittance to ICU among 36 patients were ARDS (61%), arrhythmias (44%), and shock (31%).5

CARDIOVASCULAR SEQUELAE AND TREATMENT CHALLENGES in COVID-19 PATIENT

Myocardial Injury in COVID-19 Infection
Myocardial injury happens in 7 to 28 percent of hospitalized patients with COVID-19 infection and related to poor prognosis.10,11 Patient with myocardial injury have stunning death rates compared to the one who does not (51.2 vs 5.5 percent; hazard ratio 4.26, CI 95% 1.92-9.49).6,7

Diagnosis of myocardial injury should be suspected in patients with COVID-19 infections if there are new findings of troponin elevation, global or regional left ventricular wall motion abnormalities, unexplained cardiac arrhythmias, or ECG changes (prominently diffuse ST elevation).
Based on the etiology, myocardial injury in COVID-19 infection may be differentiated into myocarditis, hypoxic injury, stress cardiomyopathy, ischemic injury caused by cardiac microvascular damage, epicardial coronary artery disease, and systemic inflammatory response syndrome (cytokine storm). Histopathologic tissue done in a case of COVID-19 patient showed that COVID-19 is not responsible for direct myocardial damage. However, further studies should be done to ensure the cause of myocarditis in COVID-19 infection.

Heart failure should be accounted as one of the complications (49% in patients who died and 3% in recovered patients) of COVID-19 patients. The risk factors of cardiac complications include older age, pre-existing cardiovascular diseases, and severe pneumonia. It is still unclear whether heart failure were caused by exacerbation of pre-existing conditions, such as left ventricular dysfunction, or due to new cardiomyopathy caused by COVID-19.

Serum troponin level should be checked routinely in patients hospitalized with COVID-19 infection. Mild troponin elevation (< 99th upper reference limit) usually happens in patient who survived after hospitalization, early moderate troponin elevation (exceed the 99th upper reference limit) usually seen in patients with suspected myocarditis and stress cardiomyopathy, progressive troponin elevation with rising accelerated in the second week hospitalization should warrant for impending mortality due to cytokine storm (median 18.5 days after symptom onset).

**Arrhythmia and Conduction System Disease in COVID-19 Patients**

Most of the time, COVID-19 infection does not cause the symptoms of arrhythmia directly. Mostly, the patient will be tachycardic (7.3% of cases) due to demand-related conditions such as fever or shortness of breath. There are notably several conditions that might trigger arrhythmia in COVID-19 patients: Myocarditis or myocardial ischemia, hypoxia or shock, electrolyte imbalance, receiving QT-prolonging drugs, and have underlying disease of Brugada disease.

Prevention should be done by electrocardiography (ECG) examination. Although 12 lead ECG is recommended, a single lead recording may suffice to minimize staff exposure to the patient. The thing to note is mainly the QRS-T morphology. From the QRS-T morphology, we may determine the possibility of myocarditis, acute coronary syndrome, and the baseline of QT interval. Frequent monitoring of QT interval should be done especially if COVID-19 drugs are started (Figure 1); mainly azithromycin (risk of Torsades de pointes 4.7-6.7%) and chloroquine (or hydroxychloroquine) which may increase the risk of QT prolongation and the risk of Torsades de Pointes (TdP). This was caused by activation blockage of potassium channel IKr (hERG/KV11.1) and both treatments metabolized by CYP3A4 which delay its clearance in the plasma.
Patients with known Brugada syndrome may need special attention regarding temperature management. Paracetamol use for fever control will be paramount in preventing the risk of ventricular arrhythmia due to fever in COVID-19 patients with Brugada Syndrome. In several cases, implantable cardiac defibrillator might be imperative to prevent sudden cardiac death in patient with Brugada Syndrome especially in the midst of COVID-19 pandemic.16

Viral myocarditis is known to be the main causes of arrhythmogenicity causing any degree of atrioventricular block, bundle branch blocks, or tachyarrhythmias.17,18 This especially in the acute phase due to direct cytopathic effect, gap junction dysfunction, and abnormal calcium pump along with channel function.19 Treatment relies on the type of arrhythmias such as amiodarone, beta-blocker, or even transcatheter ablation if the tachyarrhythmia was drug-resistant.20,21

**Coronary Artery Disease and Acute Coronary Syndrome in COVID-19 Patients**

About 4.2 to 25 percent of patients with COVID-19 infections had coronary artery disease (CAD).22 Although COVID-19 might not directly cause CAD, it might worsen in patient with pre-existing CAD due to increase in metabolic demand which in turn trigger type II myocardial ischemia (MI).23,24

Although type II MI dominates the presentation of acute coronary syndrome in COVID-19 patients, type I MI still exists and requires optimal management. In patients infected with COVID-19, establishing the diagnosis of ST Elevation Myocardial Infarct (STEMI) may prove to be difficult. This is related to the possibility of concomitant myocarditis in COVID-19 patients.

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**Figure 1.** Algorithm to prevent TdP or SCD in COVID-19 patients

TdP: Torsades des Pointes; SCD: Sudden Cardiac Death

Modified from: Wu CI, et al20

Baseline ECG examination
Check Baseline Electrolyte

**If..**

- QTC ≤ 500 msec (narrow QRS)
- QTC < 550 msec (wide QRS)

May give Hydroxychloroquine +/- Azithromycin

ECG Assessment within 4 hour, if:
1. QTC ≤ 500 msec (narrow QRS)
2. QTC < 550 msec (wide QRS)
3. Increase in QTC > 60 ms
4. Presence of ventricular extrasystole

**Yes**

**Risk benefit assessment vs risk of TdP/SCD**

- QTC > 500 msec (narrow QRS)
- QTC ≥ 550 msec (wide QRS)

**Daily assessment of ECG**
1. QTC ≤ 500 msec (narrow QRS)
2. QTC < 550 msec (wide QRS)
3. Increase in QTC > 60 ms
4. Presence of ventricular extrasystole

**No**
patients which is one of the differential diagnosis of STEMI patients. Although, finding regional wall motion abnormalities through point of care bedside echocardiography in the acute setting might prove to be beneficial for determining the diagnosis.  

Management of STEMI revascularization strategy might shift from primary percutaneous coronary intervention to the more liberal use of fibrinolytic therapy. This is recommended as to reduce the viral exposure to health care providers. Although, usually within 3 to 24 hours the patient may still require coronary angiography as part of pharmacoinvasive strategy. But this might differ based on the availability from each center. Similar approach also applies in Non-ST Elevation Acute Coronary Syndrome (NSTEACS) when urgent catheterization is considered. The resource limitation and risk of exposure to medical personnel should also be taken into account. 

Cardiogenic Shock

Although the available data showed the incidence of profound cardiogenic shock is low in COVID-19, the clinical presentation of COVID-19 can resemble a cardiogenic condition, therefore it is important to consider cardiogenic or mixed causes of the clinical manifestations. To distinguish ARDS and cardiogenic causes, the Berlin criteria considers symptom onset, bilateral pulmonary opacities, and lack of volume overload. Serum brain natriuretic peptide (BNP) and echocardiography can further distinguish the two. If a clear diagnosis could not be made yet, pulmonary artery catheterization can be considered when deciding for the use of extracorporeal membrane oxygenation (ECMO) or other invasive management to achieve the highest benefit for patients and the community. In patients with acute systolic heart failure and COVID-19, when inotropic support fails, intra-aortic balloon pump is recommended because of the relatively low maintenance needed. 

DRUG THERAPY AND COVID-19: INTERACTION AND CARDIOVASCULAR IMPLICATIONS

Curative Treatment of COVID-19 and The Cardiovascular Implication

Hydroxychloroquine, Chloroquine, and Azithromycin have been declared as potential prophylaxis or treatment for COVID-19 infection. Hydroxychloroquine act on the entry and post-entry stages of COVID-19 infection, likely via effects on endosomal pH and the resulting under-glycosylation of ACE-2 receptors that are required for viral entry. Both of chloroquine and hydroxychloroquine are known to prolong QT interval. They can provoke pro-arrhythmia via mechanisms beyond the block of I_{Kr} implicated in usual cases of torsade de pointes. Azithromycin, a frequently used macrolide antibiotic, lacks strong pharmacodynamic evidence of I_{Kr} inhibition. There is limited data evaluating the safety of combination therapy. Regarding a quasi-randomized comparative study by Barbosa et al (2020), stated that hydroxychloroquine did not appear to have a beneficial effect on meaningful clinical outcome measures of mortality, lymphopenia reconstitution, neutrophil-to-lymphocyte ratio, or risk for intubation. 

The AHA, the ACC and the HRS guidance for health care professionals includes additional mechanisms to reduce the risk of arrhythmias if hydroxychloroquine, chloroquine, and/ or azithromycin should be administered.  

1. Electrocardiographic/QT interval monitoring (Figure 1).
   a. Withhold hydroxychloroquine and azithromycin in patients with baseline QT prolongation (e.g. QTc ≥500 msec) or with known congenital long QT syndrome.
   b. Monitor cardiac rhythm and QT interval; withdrawal of hydroxychloroquine and azithromycin if QTc exceeds a present threshold of 500 msec.
c. In patients critically ill with COVID-19 infection, frequent caregiver contact may need to be minimized, so optimal electrocardiographic interval and rhythm monitoring may not be possible.

2. Correction of hypokalemia >4mEq/L and hypomagnesemia >2mg/dL.

3. Avoid other QTc prolonging agents whenever feasible

According to Tisdale et al (2016), there are risk factors associated with QTc prolongation, which have been developed into a risk score tool (Table 1) that takes age, sex, diuretic use, potassium level, baseline QTc, acute myocardial infarction, use of QTc prolonging drugs, sepsis and heart failure into account.\(^\text{33}\)

Another issue to be underlined is the possible drug-drug interaction with anticoagulants which are routinely used in acute coronary syndrome and as the newest emerging clinical evidence, prophylaxis for pulmonary embolism in COVID-19 patients. The use of novel oral anticoagulant (NOAC) and vitamin k-antagonist should be withheld due to the drug-drug interaction to azithromycin and hydroxychloroquine. Instead, low molecular weight heparin (LMWH), factor Xa inhibitor, and unfractionated heparin should be the drug of choice.\(^\text{34}\)

**Renin-Angiotensin-Aldosterone System Inhibitors and Aggravating the Disease Virulence Issues**

There has been a concern regarding the safety of Angiotensin Converting Enzyme inhibitor (ACEi) and Angiotensin II Receptor Blockers (ARBs) during the ongoing COVID-19 pandemic. These agents upregulate expression of ACE-2 in various tissues, including on cardiomyocytes.\(^\text{35}\) Since SARS-CoV2 binds to ACE-2 to gain entry into human cells, there is a potentially increased risk of developing COVID-19 or developing more severe disease in patients who are already on background treatment with ACEi or ARB.

Unfortunately, data showing the effects of ACEi, ARBs, and other RAAS inhibitors on lung-specific expression of ACE-2 in experimental animal models and in humans are lacking.\(^\text{35}\)

At the same time, abrupt withdrawal of RAAS inhibitors in high-risk patients, including those who have heart failure or myocardial infarction or hypertension, may result in clinical instability and adverse health outcomes. Therefore, several leading professional societies have strongly urged to not discontinue clinically-indicated ACEi/ARBs therapy in COVID-19 patients.\(^\text{36,37}\)

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Table 1. Risk score for identifying patients at greatest risk of QTc interval prolongation.
(modified from Tisdale et al.)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥68 years</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>1</td>
</tr>
<tr>
<td>Serum potassium ≤3.5 mmol/L</td>
<td>2</td>
</tr>
<tr>
<td>Presenting QTc interval ≥450 ms</td>
<td>2</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>2</td>
</tr>
<tr>
<td>Heart failure with reduced ejection fraction</td>
<td>3</td>
</tr>
<tr>
<td>1 QTc interval-prolonging drug*</td>
<td>3</td>
</tr>
<tr>
<td>≥2 QTc interval-prolonging drug*</td>
<td>3</td>
</tr>
<tr>
<td>Sepsis*</td>
<td>3</td>
</tr>
<tr>
<td>Maximum score</td>
<td>21</td>
</tr>
</tbody>
</table>

Risk score category: low risk ≤7; moderate risk = 7-10; high risk ≥11
*Three points for 1 QTc interval-prolonging drug; 3 additional points for ≥2 QTc interval-prolonging drug (total 6 points).
^During acute event/disease

Conclusion
Cardiovascular disease may present as one of the comorbidities for COVID-19 infection or even as a complication of COVID-19. ACE inhibition, as the holy grail of heart failure therapy; although debatable regarding its use in COVID-19 infection, it was recommended and proven beneficial in COVID-19 patients with hypertension or heart failure. Furthermore, the use of COVID-19 medications has the risk of malignant arrhythmia and drug-drug interactions. Those facts should raise the awareness of cardiovascular disease in the midst of COVID-19 pandemic infection.

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We the Authors of this manuscript declare that we have received the proper permission regarding the use of figures/images/illustrations from their Original Authors

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