



What is Important in Patients with COVID-19 Associated with Myocardial Infarction?

Dear editor,

The utilization of various kinds of therapeutic strategies for the treatment of patients infected with coronavirus disease-2019 (COVID-19) is a topic of great interest to researchers the world over. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and represents the causative agent of a lethal disease that is a great global health concern.¹ Since its identification in December 2019 in Wuhan, Hubei Province, China, COVID-19 has spread rapidly throughout the world.² The World Health Organization announced the pandemic outbreak of COVID-19 on February 11, 2020, as the infection had affected over 100 countries in a matter of weeks.³ This disease begins with flu-like symptoms such as fever, dry cough, myalgia, and viral pneumonia and can progress to acute respiratory distress syndrome and myocarditis.⁴

Among different patients, those with cardiovascular disorders, immune system defects, diabetes, and hypertension are at high risk for infection with SARS-CoV-2.⁵ Myocardial infarction (MI) is the most important entity. Activated inflammation in the vascular wall by severe viral infections such as SARS or influenza can increase the risk of plaque rupture and thrombus formation, inducing either ST-elevation MI or non-ST-elevation MI in susceptible patients.^{6,7} A previous study indicated that acute MI was the cause of death in 2 of 5 fatal cases involved with SARS.⁸ Another investigation showed that the influenza virus could lead to an increased risk of acute MI.⁹ Although reports on MI in patients with SARS-CoV-2 have not been published yet,¹ research indicates that due to extensive inflammation and hypercoagulability, the risk of acute MI may be present in patients with SARS-CoV-2.¹⁰

There are 2 important issues concerning patients with SARS-CoV-2 with respect to the association between the infection and MI. The first issue is the higher rate of mortality in patients with a preexisting cardiovascular disease who are infected with SARS-CoV-2, especially when it is complicated by MI.¹¹ The precise mechanisms of cardiovascular injury related to COVID-19 have not been fully explored and are likely multifactorial including accelerated aging, immune system dysregulation,¹² and the pathogenic mechanism associated with angiotensin-converting enzyme 2 (ACE2) receptors. Extensive research has underscored the pivotal

role played by ACE2 receptors as functional receptors for SARS-CoV-2 since they are highly expressed in myocardial and lung alveolar cells.¹³ According to single-cell RNA sequencing via reverse transcription-polymerase chain reaction (RT-PCR), more than 7.5% of myocardial cells have positive ACE2 expression, which can provide a suitable site for the binding of the spike proteins of SARS-CoV-2.² This interaction between ACE2 receptors and spike proteins in myocardial cells can trigger a cytokine storm and ultimately lead to vascular inflammation, plaque instability, myocardial inflammation, and myocardial suppression.^{13,14}

The second important issue is the controversy surrounding the therapeutic strategy for MI in patients infected with SARS-CoV-2. There is as yet no specific treatment protocol for the treatment of this infection, with various pharmacologic agents being under active investigation. Supportive treatment with remdesivir, ribavirin, lopinavir/ritonavir, favipiravir, antimalarials (eg, chloroquine and hydroxychloroquine), azithromycin, corticosteroids, and biologics (eg, tocilizumab) has been administered to these patients.^{10,15} It is important to consider that the interactions between these drugs and other cardiovascular medications such as antihypertensives, antiarrhythmics, anticoagulants, antiplatelets, and statins could increase the side effects of the drugs, especially in patients with MI.³ On the other hand, medications such as lopinavir/ritonavir can cause QT and PR-interval prolongation, which may be more hazardous in MI patients infected with SARS-CoV-2 since they have inherent electrical disturbances.^{16,17} Chloroquine and hydroxychloroquine affect the intracellular pH level, which leads to electrolyte abnormalities, cardiotoxicity, and prolonged QT intervals.¹⁸ The administration of azithromycin in patients with heart disorders who are infected with SARS-CoV-2 could interfere with anticoagulants, statins, antiarrhythmics, and other QT-prolonging agents, which might lead to torsades de pointes.¹⁶ The concurrent consumption of the aforementioned medications by MI patients with SARS-CoV-2 seems injudicious. It is, therefore, vital that new drugs be introduced into the current pharmacologic armamentarium for the management of this special group.

Research has been conducted to find potent drugs with fewer side effects. Cavagna et al,¹⁹ in a monocentric cross-sectional study, used calcineurin-inhibitors in the treatment of SARS-CoV-2-infected cases with organ transplantation or rheumatic diseases. They posited that the use of calcineurin inhibitor-based immunosuppressive regimens such as tacrolimus could be considered a safe therapeutic option for SARS-CoV-2 because they are capable of suppressing the phosphatase activity of calcineurin and result in decreased interleukin-2 production. Another investigation



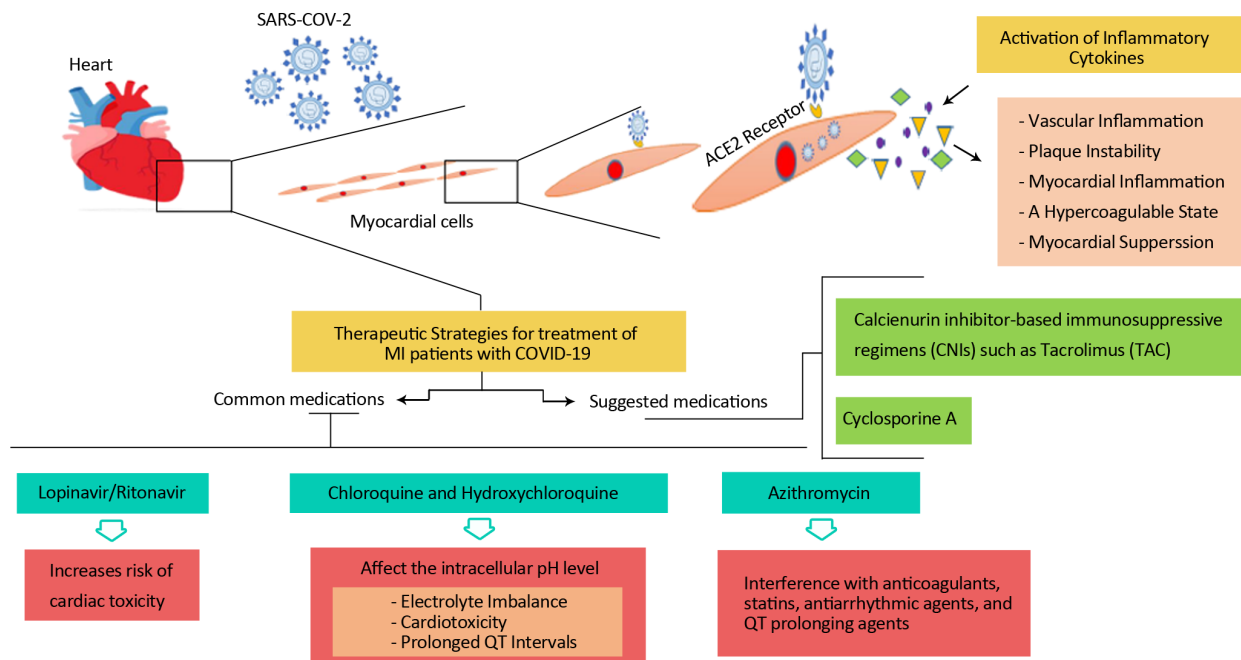


Figure 1. Possible mechanisms of cardiovascular injury due to COVID-19 and therapeutic strategies for the treatment of MI patients with COVID-19
 SARS-COV-2, Severe acute respiratory syndrome coronavirus 2; ACE2, Angiotensin-converting enzyme 2; MI, Myocardial infarction; CNI, Calcineurin inhibitor; TAC, Tacrolimus; QT, Quiet Torpedo

suggested that cyclosporine, which is a commonly-used and well-tolerated drug approved by the FDA, be used as a treatment candidate in patients with MI on the strength of its cardioprotective positive effects.²⁰ Cyclosporine is presumed to confer cytoprotection by inhibiting the opening of the mitochondrial permeability transition pore (MPTP) and stabilizing the inner mitochondrial membrane by preventing cyclophilin D from binding to the adenine nucleotide translocator, which could be useful in patients with MI who are infected with SARS-CoV-2.²¹

In conclusion, in this letter, as is depicted by the figure below, we have focused on 2 important issues: the possible risk of MI in patients who are infected with SARS-CoV-2 and the different therapeutic protocols that are currently applied for their management. We have also highlighted the need for the replacement of these protocols with safer ones given the risk they may pose to this group of patients. Calcineurin inhibitors and cyclosporine are more likely to have fewer cardiac side effects in MI patients infected with SARS-CoV-2. Indubitably, however, both calcineurin inhibitors and cyclosporine require extensive clinical trials for the further evaluation of their effects in such patients.

References

1. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475-481.
2. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, MacLaren G, Brodie D, Shekar K. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med* 2020;8:518-526.
3. Xu B, Kraemer MUG; Open COVID-19 Data Curation Group. Open access epidemiological data from the COVID-19 outbreak. *Lancet Infect Dis* 2020;20:534.
4. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270-273.
5. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, Chen Y, Han Y. Cardiovascular manifestations and treatment considerations in COVID-19. *Heart* 2020;106:1132-1141.
6. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* 2018;72:2231-2264.
7. Warren-Gash C, Hayward AC, Hemingway H, Denaxas S, Thomas SL, Timmis AD, Whitaker H, Smeeth L. Influenza infection and risk of acute myocardial infarction in England and Wales: a CALIBER self-controlled case series study. *J Infect Dis* 2012;206:1652-1659.
8. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS, Chan KH, Ng JS, Zheng BJ, Ng WL, Lai RW, Guan Y, Yuen KY; HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of



- coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003;361:1767-1772.
9. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, Katz K, Ko DT, McGeer AJ, McNally D, Richardson DC, Rosella LC, Simor A, Smieja M, Zahariadis G, Gubbay JB. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med* 2018;378:345-353.
 10. Chary MA, Barbuto AF, Izadmehr S, Hayes BD, Burns MM. COVID-19: Therapeutics and their toxicities. *J Med Toxicol* 2020;16:284-294.
 11. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020 Jul 1;5:802-810.
 12. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:811-818.
 13. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, Mou HM, Wang LH, Zhang HR, Fu WJ, Luo T, Liu F, Guo QN, Chen C, Xiao HL, Guo HT, Lin S, Xiang DF, Shi Y, Pan GQ, Li QR, Huang X, Cui Y, Liu XZ, Tang W, Pan PF, Huang XQ, Ding YQ, Bian XW. A pathological report of three COVID-19 cases by minimal invasive autopsies. *Zhonghua Bing Li Xue Za Zhi* 2020;49:411-417.
 14. Levi M, van der Poll T, Büller HR. Bidirectional relation between inflammation and coagulation. *Circulation* 2004;109:2698-2704.
 15. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020;323:1824-1836.
 16. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, Brown TS, Der Nigoghossian C, Zidar DA, Haythe J, Brodie D, Beckman JA, Kirtane AJ, Stone GW, Krumholz HM, Parikh SA. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol* 2020;75:2352-2371.
 17. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med* 2020;38:1504-1507.
 18. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care* 2020;57:279-283.
 19. Böhm M, Frey N, Giannitsis E, Sliwa K, Zeiher AM. Coronavirus disease 2019 (COVID-19) and its implications for cardiovascular care: expert document from the German Cardiac Society and the World Heart Federation. *Clin Res Cardiol* 2020;109:1446-1459.
 20. Rudnicka L, Glowacka P, Goldust M, Sikora M, Sar-Pomian M, Rakowska A, Samochocki Z, Olszewska M. Cyclosporine therapy during the COVID-19 pandemic. *J Am Acad Dermatol* 2020;83:e151-152.
 21. Bünger R, Mallet RT. Cyclosporine A cardioprotection: mechanisms and potential for clinical application. *Crit Care Med* 2013;41:1156-1158.

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