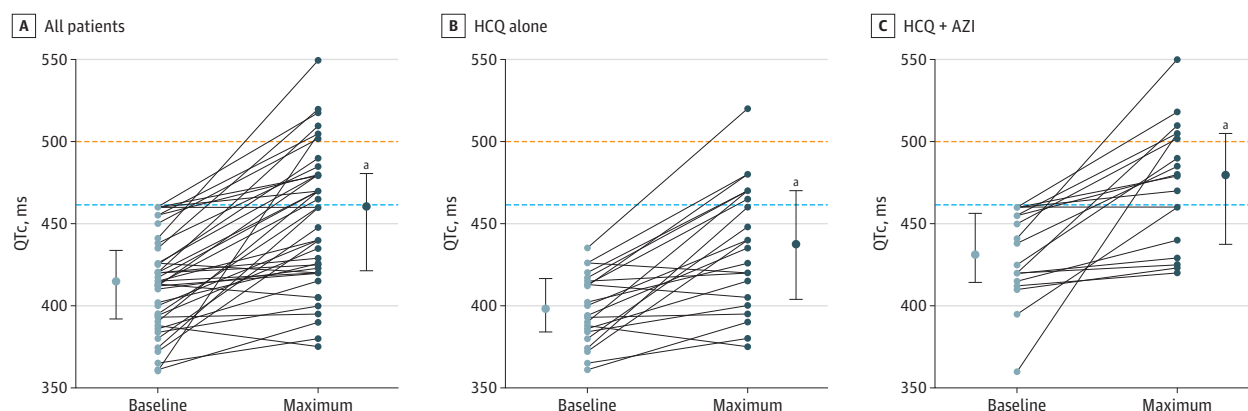Figure. Individual Baseline and Maximal Corrected QT Interval Values in Patients With Coronavirus Disease 2019 (COVID-19) Treated With Hydroxychloroquine and Azithromycin

Individual baseline (pretreatment) and maximal corrected (QTc) interval values are shown for 40 critically ill patients with COVID-19 treated with hydroxychloroquine alone (22 [55.0%]) or in association (18 [45.0%]) with azithromycin. Median and interquartile range values of QTc before and after the start of hydroxychloroquine/azithromycin. Horizontal blue and orange dashed lines represent the upper normal value of the QTc interval (460 milliseconds) and the QTc cutoff value of 500 milliseconds (high risk of ventricular arrhythmia).

[a] $P < .01$.

of patients raises concerns about the widespread use of hydroxychloroquine, with or without azithromycin, to treat COVID-19 in settings where patients cannot be adequately monitored.

Francis Bessière, MD, PhD
Hugo Roccia, MD
Antoine Delinière, MD
Rome Charrière, MD
Philippe Chevalier, MD, PhD
Laurent Argaud, MD, PhD
Martin Cour, MD, PhD

Author Affiliations: Hospices Civils de Lyon, Hôpital Cardiologique Louis Pradel, Service d'électrophysiologie et de Stimulation Cardiaque, Université de Lyon, Lyon, France (Bessière, Delinière, Chevalier); Hospices Civils de Lyon, Hôpital Cardiologique Louis Pradel, Centre de Référence National des Troubles du Rythme Cardiaque d'origine Héréditaire, Lyon, France (Bessière, Delinière, Chevalier, Cour); Hospices Civils de Lyon, Hôpital Edouard Herriot, Médecine Intensive - Réanimation, Lyon, France (Roccia, Argaud); Centre Hospitalier de Valence, Service de Maladies Infectieuses, Valence, France (Charrière).

Accepted for Publication: April 14, 2020

Corresponding Author: Martin Cour, MD, PhD, Médecine Intensive-Réanimation, Hôpital Edouard Herriot, 5, Place d'Arsonval, 69437 Lyon Cedex 03, France (martin.cour@chu-lyon.fr).

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. Published online February 24, 2020. doi:10.1001/jama.2020.2648

2. Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. *Science*. 2020;367(6485):1412-1413. doi:10.1126/science.367.6485.1412

3. Mahase E. Covid-19: six million doses of hydroxychloroquine donated to US despite lack of evidence. *BMJ*. 2020;368:m1166. doi:10.1136/bmj.m1166

4. Drew BJ, Ackerman MJ, Funk M, et al; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121(8):1047-1060. doi:10.1161/CIRCULATIONAHA.109.192704

5. Yazdany J, Kim AHJ. Use of Hydroxychloroquine and chloroquine during the COVID-19 pandemic: what every clinician should know. *Ann Intern Med*. Published online March 31, 2020. doi:10.7326/M20-1334

6. Etchegoyen CV, Keller GA, Mrad S, Cheng S, Di Girolamo G. Drug-induced QT interval prolongation in the intensive care unit. *Curr Clin Pharmacol*. 2017;12(4):210-222. doi:10.2174/1574884713666180223123947

COMMENT & RESPONSE

Myocardial Injury in COVID-19—Can We Successfully Target Inflammation?

To the Editor One of the most intriguing issues that rapidly arose in the clinical management of patients with coronavirus disease 2019 (COVID-19) was concurrent myocardial injury with or without corresponding symptoms. Therefore, we read with

great interest the work by Guo et al,[1] which presented valuable data regarding the significance of cardiac involvement in patients with COVID-19. Remarkably, in this cohort of 187 patients, those without known underlying cardiovascular disease (CVD) but with myocardial injury had worse outcomes compared with those with underlying CVD but normal troponin levels.[1] Furthermore, N-terminal pro–B-type natriuretic peptide kinetics suggested a potentially clinically significant association with cardiac function beyond merely biochemical myocardial injury.[1]

These findings, combined with the observed positive correlation of troponin level with C-reactive protein level, were interpreted as a potential indication that, among other mechanisms such as hypoxemia, the COVID-19–related inflammatory cascade could affect the myocardium directly. In a study by our research group,[2] inhibition of inflammation by colchicine was associated with significant cardioprotective effects (evaluated both by total troponin output and magnetic resonance imaging) in the context of acute myocardial infarction. Colchicine effects include inhibition of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which is presumed to be involved in ischemia-reperfusion injury.[3] Interestingly, severe acute respiratory syndrome coronavirus (SARS-CoV) infection has been implicated with NLRP3 inflammasome activation[4]; notably, SARS-CoV and SARS-CoV-2 are highly homologous in genome.[1] On the basis of this pathophysiological premise and given the negative prognostic significance of COVID-19–related myocardial injury and other inflammation-related complications, we have proposed the use of colchicine in this context and are going to evaluate it in a prospective randomized study (ClinicalTrials.gov identifier: NCT04326790).

Undeniably, in view of the findings of Guo et al,[1] the importance of effective myocardial injury prevention will be even greater in the subset of patients with COVID-19 and known CVD, who in this cohort presented with the highest mortality. The issue in question here is whether we will be able to do the obvious—that is, could we use treatments specifically targeting the COVID-19–associated inflammation storm to improve outcomes or even just buy time for our patients? "The true mystery of the world is the visible, not the invisible."[5]

Georgios Giannopoulos, MD, PhD
Dimitrios A. Vrachatis, MD, MSc, PhD
Spyridon G. Deftereos, MD, PhD

Author Affiliations: General Hospital of Athens "G.Gennimatas," Athens, Greece (Giannopoulos); Department of Cardiovascular Medicine, Humanitas Clinical and Research Hospital, Milan, Italy (Vrachatis); Attikon Hospital, 2nd Department of Cardiology, National and Kapodistian University of Athens Medical School, Athens, Greece (Deftereos).

Correspondence Address: George Giannopoulos, MD, PhD, General Hospital of Athens "G.Gennimatas," 154 Mesogeion Ave, Athens 11527, Greece (ggiann@med.uoa.gr).

1. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1017

2. Deftereos S, Giannopoulos G, Angelidis C, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. *Circulation*. 2015; 132(15):1395-1403. doi:10.1161/CIRCULATIONAHA.115.017611

3. Kawaguchi M, Takahashi M, Hata T, et al. Inflammasome activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury. *Circulation*. 2011;123(6):594-604. doi:10.1161/CIRCULATIONAHA.110.982777

4. Wang H, Naghavi M, Allen C, et al; GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053): 1459-1544. doi:10.1016/S0140-6736(16)31012-1

5. Wilde O. *The Picture of Dorian Gray*. Gillespie MP, ed. 2nd ed. W. W. Norton & Co; 2006.

In Reply Myocardial injury as indicated by elevated serum troponin levels has been detected in many patients with coronavirus disease 2019 (COVID-19), with significant differences having been noted between patients who died and survived.[1] Our recent study suggested that patients with underlying cardiovascular disease (CVD) were more prone to experience myocardial injury and faced a higher risk of death during the course of COVID-19 compared with patients without underlying CVD.[1] For patients with underlying CVD, such as hypertension, coronary artery disease, and cardiomyopathy, viral infection can further damage myocardial cells possibly through several mechanisms, including direct damage by virus, systemic inflammatory response, destabilized coronary plaque, and aggravated hypoxia.

The exact pathophysiological mechanism underlying myocardial injury caused by COVID-19 is not fully understood; important causes may be via direct damage of myocardial cells by the virus and by the systemic inflammation. In our recent study,[1] plasma troponin T levels exhibited a significant positive linear correlation with plasma high-sensitivity C-reactive protein levels, indicating that myocardial injury may be closely associated with inflammatory pathogenesis during the progress of disease. Laboratory parameters in our study showed that the level of lymphocytes was reduced in most patients with COVID-19. This suggests that viral infection may mainly act on lymphocytes, especially T lymphocytes, similar to the situation of severe acute respiratory syndrome coronavirus (SARS-CoV), notably because SARS-CoV-2 and SARS-CoV are highly homologous in genome. Recent data showed that 52% of patients infected with COVID-19 had elevated interleukin 6 levels and 86% had elevated C-reactive protein levels.[2] This indicates a significant inflammatory state in patients with COVID-19. Huang et al[3] highlighted that in patients with COVID-19, the imbalance of Th1 and Th2 responses resulted in a cytokine storm, which may contribute to myocardial injury.

Accordingly, as for the issue in question raised by Giannopoulos et al whether we could use treatments specifically targeting the COVID-19–associated inflammation storm to improve outcomes, as known to all, no approved preventive vaccines or specific therapies are available for COVID-19 at present. However, the exaggerated inflammatory cell infiltration and cytokine release after infection may cause reduction in coronary blood flow, decreases in oxygen supply, destabilization of coronary plaque, and microthrombogenesis.

Hence, we speculated that patients with COVID-19 might benefit from treatments specifically targeting the COVID-19-associated inflammation storm. Indeed, in addition to antiviral medications, numerous immune-modulating medications to regulate inflammatory response are currently being investigated in patients with COVID-19. In clinical practice, glucocorticoid is generally used to inhibit severe inflammation in high-risk patients. Besides, chloroquine, which has been used as an antimalarial agent, blocks virus infection by increasing the endosomal pH required for virus/cell fusion and has been demonstrated in vitro to have inhibitory activity in SARS-CoV-2.[4] Yet, for patients with COVID-19 experiencing an inflammation storm, more evidence is needed to verify the effectiveness of glucocorticoid and immunosuppressive therapy. For us, it may be reasonable to triage patients with COVID-19 according to the presence of underlying CVD and evidence of myocardial injury for prioritized treatment and particularly for treatments specifically targeting on inflammation.

Yongzhen Fan, MD
Tao Guo, MD
Zhibing Lu, MD

Author Affiliations: Department of Cardiology, Zhongnan Hospital of Wuhan University, Wuhan, China.

Corresponding Author: Zhibing Lu, MD, Department of Cardiology, Zhongnan Hospital of Wuhan University, 169 E Lake Rd, Hubei 430071, China (luzhibing222@163.com).

1. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1017

2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513. doi:10.1016/S0140-6736(20)30211-7

3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5

4. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72-73. doi:10.5582/bst.2020.01047

CORRECTION

Errors in Abstract, Results, and End Matter: The Brief Report "Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19),"[1] published online on May 1, 2020, contained 3 errors. The first was a misstated percentage in the Abstract and Results. The phrase "3 patients (3%)" should have said "3 patients (8%)." In addition, a percentage in the Results section was missing a decimal point. The phrase "(26 patients [289%]…)" should have said "(26 patients [28.9%]…)." Finally, the Corresponding Author information for Howard S. Gold, MD, and Peter J. Zimetbaum, MD, was inadvertently omitted and has been added. The article has been corrected online.

1. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. Published online May 1, 2020. doi:10.1001/jamacardio.2020.1834

Errors in Table 2: In the Original Investigation titled "Safety and Efficacy of Femoral Access vs Radial Access in ST-Segment Elevation Myocardial Infarction: The SAFARI-STEMI Randomized Clinical Trial,"[1] published in the February issue of *JAMA Cardiology*, data were incorrectly shown for the type of stent and for 2 of the critical time intervals in Table 2. In the "Radial Access" column, the No./total No. (%) was changed to 912/1043 (87.4%) for drug-eluting stents, 123/1043 (11.8%) for bare metal stents, and 8/1043 (0.8%) for both, and the median (interquartile range) critical time interval was changed to 189 (136-300) minutes for "Symptom onset to first balloon inflation/device" and 48 (36-64) minutes for "Arrival at PCI [percutaneous coronary intervention] center to first balloon inflation/device." In the "Femoral Access" column, the No./total No. (%) was changed to 952/1076 (88.5%) for drug-eluting stents, 113/1076 (10.5%) for bare metal stents, and 11/1076 (1.0%) for both, and the median (interquartile range) critical time interval was changed to 185 (132-301) minutes for "Symptom onset to first balloon inflation/device" and 46 (34-61) minutes for "Arrival at PCI center to first balloon inflation/device." Finally, the *P* value for table footnote c in Table 2 should be changed to *P* = .003. This article has been corrected online. This article was previously corrected to fix an incorrect degree for the second author in the byline.

1. Le May M, Wells G, So D, et al. Safety and efficacy of femoral access vs radial access in ST-segment elevation myocardial infarction: the SAFARI-STEMI randomized clinical trial. *JAMA Cardiol*. 2020;5(2):126-134. doi:10.1001/jamacardio.2019.4852

Error in Text: The Viewpoint "Fear of Coronavirus Disease 2019—An Emerging Cardiac Risk,"[1] published online July 22, 2020, contained an error in the text. The phrase "there are no specific therapies that are known to decrease mortality" should instead have said "there are as yet no specific therapies broadly accepted to decrease mortality." The error has been corrected online.

1. Wessler BS, Kent DM, Konstam MA. Fear of coronavirus disease 2019—an emerging cardiac risk. *JAMA Cardiol*. Published online July 22, 2020. doi:10.1001/jamacardio.2020.2890