ESC European Society of Cardiology
European Heart Journal (2020) **41**, 3836–3838
doi:10.1093/eurheartj/ehaa727

EDITORIAL

The significance of COVID-19-associated myocardial injury: how overinterpretation of scientific findings can fuel media sensationalism and spread misinformation

Nikolaos G. Frangogiannis *

The Wilf Family Cardiovascular Research Institute, Department of Medicine (Cardiology), Albert Einstein College of Medicine, 1300 Morris Park Avenue, Forchheimer G46B, Bronx, NY 10461, USA

Online publish-ahead-of-print 2 October 2020

This editorial refers to 'Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study'†, by C. Basso *et al.*, on page 3827.

Evidence of myocardial injury is found in a significant fraction of hospitalized coronavirus disease 2019 (COVID-19) patients. Elevation of serum troponins, the most common COVID-19-associated myocardial abnormality, is found predominantly in patients with underlying cardiovascular disease, and is associated with increased mortality.[1,2] Whether biochemical evidence of myocardial injury reflects primary severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-mediated cardiac disease or secondary consequences of demand ischaemia remains unknown. Although it has been suggested that SARS-CoV-2 may gain entry into cardiomyocytes by binding to the abundant angiotensin-converting enzyme 2 (ACE2) expressed on the cell membrane, evidence supporting the role of myocarditis in COVID-19 myocardial pathology remains scant. Importantly, characterization of the pathological myocardial changes in COVID-19 patients is limited to case reports and small case series.[3,4]

In the current issue of the *European Heart Journal*, Basso and co-workers[5] provide the first systematic histopathological analysis of the myocardial alterations in patients dying from COVID-19. In an international multicentre study, the authors assessed cardiac pathology in 21 consecutive autopsies. The mechanism of death for the majority of the patients was adult respiratory distress syndrome (ARDS). All but one of the patients had underlying conditions known to cause cardiac remodelling, including a prior history of ischaemic heart disease, hypertension, diabetes, and renal failure. The authors report that 86% of the patients exhibited widespread myocardial macrophage infiltration. A small fraction of patients (14%) had changes consistent with lymphocytic myocarditis, defined as the presence of multifocal inflammatory infiltrates associated with cardiomyocyte injury, not due to some other cause. Evidence of a recent myocardial infarction was found in one patient, whereas microvascular thrombi were noted in four patients. The study highlights the broad spectrum of cardiac injury patterns noted in critically ill COVID-19 patients, that may include acute coronary events, microvascular thrombosis, and myocardial inflammation. However, the study also has significant limitations. First, the findings cannot be generalized to all COVID-19 patients, but only represent subjects who died of the disease due to respiratory failure. Secondly, relationships between myocardial pathology and perturbations of systolic or diastolic function were not studied. Thirdly, the study cannot establish a causative relationship between SARS-CoV-2 and myocardial inflammation. Older patients with hypertension, diabetes, chronic renal failure, and chronic ischaemic heart disease often exhibit chronic low level myocardial inflammatory activation associated with interstitial macrophage infiltration.[6,7] Due to the absence of a control group with comorbidities comparable with the COVID-19 patient population, the role of the viral infection in the pathogenesis of the myocardial changes cannot be determined. Interpretation is further complicated by the potential impact of demand ischaemia, due to fever and tachycardia typically associated with respiratory failure, on myocardial pathology. Moreover, in the absence of molecular evidence documenting the presence of the virus, the lymphocytic infiltrate found in a small

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.
† doi:10.1093/eurheartj/ehaa664.
* Corresponding author. Tel: +1 718 430 3546, Fax: +1 718 430 8989, Email: nikolaos.frangogiannis@einstein.yu.edu

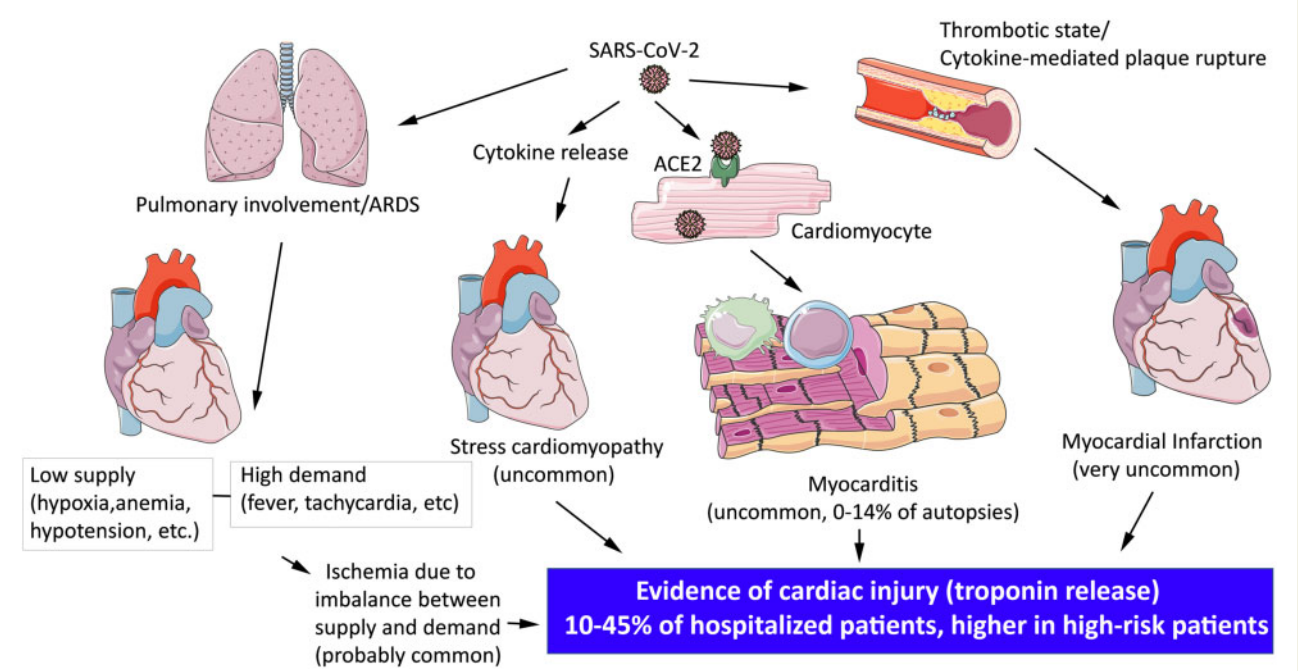

Figure 1 The causes of COVID-19-associated cardiac injury in adult patients. In hospitalized COVID-19 patients, myocardial injury defined as release of troponins is common (found in 10–45% of patients), and is found predominantly in critically ill individuals with comorbid conditions. Although it has been suggested that SARS-CoV-2 may enter ACE2-expressing cardiomyocytes and cause direct injury, current evidence suggests that COVID-19-associated myocarditis is uncommon, even in patients who succumb to the disease. In the majority of patients with COVID-19-related myocardial disease, cardiomyocyte injury probably reflects the imbalance between myocardial supply and demand due to the consequences of the critical illness, amplified by pre-existing cardiovascular disease. Cytokine storm-mediated cardiac depression may also represent an uncommon cause of myocardial injury in COVID-19 patients. Moreover, it has been suggested that activation of a thrombotic state, vascular inflammation, and release of cytokines may precipitate plaque rupture in patients with pre-existing atherosclerotic disease, causing acute myocardial infarction. However, such events have rarely been documented. This cartoon was designed using Servier Medical Art (https://smart.servier.com/).

number of COVID-19 patients may not represent myocarditis. Thus, the myocardial pathological alterations observed in the current study may not reflect specific effects of the virus, but rather the consequences of critical illness in a population with a high prevalence of underlying conditions.

The findings of the current study are consistent with the notion that direct COVID-19-mediated cardiac pathology may be uncommon (*Figure 1*). In hospitalized COVID-19 patients, elevated serum troponin levels are commonly found and are more prominent in patients with underlying conditions.[8] However, biochemical evidence of cardiac injury is not unique to COVID-19. Patients with severe community-acquired pneumonia, requiring intensive care, typically exhibit increased troponin levels.[9] Increased myocardial demand due to fever and tachycardia, and reduced supply due to hypoxaemia and hypotension, can result in myocardial ischaemia in vulnerable patients, and may explain the evidence of myocardial injury commonly found in high-risk COVID-19 patients.[10] Moreover, systemic inflammatory activation leading to cytokine storm may promote dysfunction, whereas prothrombotic effects may trigger plaque rupture, precipitating coronary events.[11] The evidence documenting SARS-CoV-2 myocarditis as a cause of cardiac dysfunction is limited to case reports. In a case series studying 14 patients who succumbed to COVID-19 in Washington State, one patient with lymphocytic myocarditis and evidence of myocardial viral RNA was identified. In a study of 39 consecutive COVID-19 autopsy cases from Germany, 41% of patients had evidence of myocardial viral presence in the absence of significant inflammation.[12] The long-term significance of viral infection in COVID-19 patients remains unknown.

The authors should be complimented, not only for producing the first systematic investigation of myocardial pathological changes in COVID-19, but also for an objective and unbiased discussion that acknowledges the limitations of the study, without overinterpretations and hype. Adoption of careful and objective approaches for data interpretation and dissemination of scientific findings is critical to overcome the challenges of the pandemic. In most research fields, interest in specialized scientific articles typically remains limited within specific groups of researchers with related interests, and overinterpreted findings are filtered through the collective perspective of the scientific community. In contrast, the COVID-19 literature generates broad interest and can have an immediate impact on the public. Throughout the world, hundreds of journalists scan the COVID-19 literature; most of them have no scientific background. Considering that the attention generated by a news article, quantified by the number of readers, clicks, and comments, is a major measure of journalistic success, it is not surprising that many journalists tend to prioritize sensationalism over accuracy. As a result, overinterpreted scientific

studies can fuel sensationalist news stories, ultimately leading to misinformation of the public.

Recent dramatic headlines regarding the 'devastating' and 'lingering' consequences of COVID-19 on the myocardium illustrate this major problem. Cardiac magnetic resonance imaging in 100 patients who recovered from COVID-19 showed that the majority (78%) had subtle increases in non-specific indicators associated with inflammation (1.9% higher native T1 and an 8.3% increase in native T2) in comparison with a risk factor-matched control group that had no history of a respiratory infection.[13] All patients had normal systolic function. Despite the absence of any robust evidence of inflammatory activity, these observations were interpreted by the authors as suggestive of an 'ongoing perimyocarditis' and indicative of a 'considerable burden of inflammatory disease in large and growing parts of the population'. These statements fuelled dramatic warnings in the lay and scientific press suggesting that SARS-CoV-2 has a 'devastating impact on the myocardium', 'ravages the heart in many ways', and 'can have lasting effects on heart health' (https://www.sciencemag.org/news/2020/07/brain-fog-heart-damage-covid-19-s-lingering-problems-alarm-scientists; Supplementary material online, *Table S1*). Such sensationalist statements are currently not supported by evidence. We simply have no information on any long-term effects of SARS-CoV-2 in the heart.

Speculative discussions and dissemination of doomsday scenarios can have a major negative impact in our fight against the pandemic, not only by increasing anxiety levels and by spreading fear, but also by undermining public confidence in science. It is up to the scientific community to ensure that the messages communicated in scientific manuscripts are supported by robust evidence. Our goal should not be to publish a 'newsworthy' paper in order to attract attention, but rather to present the facts and to support data-driven conclusions.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

N.G.F.'s laboratory is supported by National Institutes of Health grants R01 HL76246, R01 HL85440, and R01 HL149407, and by U.S. Department of Defense grants PR151029 and PR181464.

Conflict of interest: none declared.

References

1. 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;**5**:802–810.
2. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, Cao S, Liu X, Xiang Y, Zhao Q, Huang H, Yang B, Huang C. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J* 2020;**41**:2070–2079.
3. Buja LM, Wolf DA, Zhao B, Akkanti B, McDonald M, Lelenwa L, Reilly N, Ottaviani G, Elghetany MT, Trujillo DO, Aisenberg GM, Madjid M, Kar B. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. *Cardiovasc Pathol* 2020;**48**:107233.
4. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, Najafian B, Deutsch G, Lacy JM, Williams T, Yarid N, Marshall DA. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet* 2020;**396**:320–332.
5. Basso C, Leone O, Rizzo S, De Gaspari M, Van der Wal AC, Aubry M-C, Bois MC, Lin PT, Maleszewski JJ, Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. *Eur Heart J* 2020;**41**:3827–3835.
6. Yoshizawa S, Uto K, Nishikawa T, Hagiwara N, Oda H. Histological features of endomyocardial biopsies in patients undergoing hemodialysis: comparison with dilated cardiomyopathy and hypertensive heart disease. *Cardiovasc Pathol* 2020;**49**:107256.
7. Frangogiannis NG, Shimoni S, Chang SM, Ren G, Shan K, Aggeli C, Reardon MJ, Letsou GV, Espada R, Ramchandani M, Entman ML, Zoghbi WA. Evidence for an active inflammatory process in the hibernating human myocardium. *Am J Pathol* 2002;**160**:1425–1433.
8. Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, Cheng Y, Yan J, Ping H, Zhou Q. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. *Int J Cardiol* 2020;**311**:116–121.
9. Frencken JF, van Baal L, Kappen TH, Donker DW, Horn J, van der Poll T, van Klei WA, Bonten MJM, Cremer OL, Members of the MARS Consortium. Myocardial injury in critically ill patients with community-acquired pneumonia. A cohort study. *Ann Am Thorac Soc* 2019;**16**:606–612.
10. Libby P. The heart in COVID19: primary target or secondary bystander? *JACC Basic Transl Sci* 2020;**5**:537–542.
11. Tomasoni D, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* 2020;**22**:957–966.
12. Lindner D, Fitzek A, Brauninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss HP, Blankenberg S, Puschel K, Westermann D. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. *JAMA Cardiol* 2020;doi:10.1001/jamacardio.2020.3551.
13. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;doi:10.1001/jamacardio.2020.3557.