2. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol*. 2020;75(18):2352-2371. doi:10.1016/j.jacc.2020.03.031

3. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. *J Thromb Haemost*. Published online April 10, 2020. doi:10.1111/jth.14828

4. Alfonso F. The "vulnerable" stent why so dreadful? *J Am Coll Cardiol*. 2008;51(25):2403-2406. doi:10.1016/j.jacc.2008.03.029

COMMENT & RESPONSE

Coronavirus Disease 2019 (COVID-19) and Cardiac Injury

To the Editor We read with great interest the important findings of Shi et al[1] exploring cardiac injury in patients with confirmed coronavirus disease 2019 (COVID-19). Approximately 20% of patients diagnosed with COVID-19 had signs of cardiac injury as measured by elevated high-sensitivity troponin I (hs-TNI) levels. Moreover, evidence of cardiac injury was associated with 4-fold increased mortality risk even after accounting for age and preexisting cardiovascular disease (CVD). Shi et al[1] acknowledged that with this severe acute respiratory infection may come cytokine storm syndrome leading to inflammation and cardiac myocyte apoptosis or necrosis.

We wish to underscore a few key points. High-sensitivity troponin I is detectable in more than 80% of the general population and, as a reflection of subclinical myocardial damage, has been shown to predict all-cause mortality even in those without CVD.[2] High hs-TNI levels within the normal range may be a marker of patients with increased vulnerability to experiencing the more severe complications resulting from the systemic inflammatory effects of COVID-19.

While elevated hs-TNI levels clearly portend poor prognosis, the question remains—why? Is hs-TNI a marker of underlying subclinical CVD that confers risk in the setting of hypoxia from profound respiratory disease or hypoperfusion from viral sepsis (ie, type 2 myocardial infarction reflecting supply/demand imbalance), both made worse in the presence of comorbidities? Is it a reflection of direct viral myocarditis or a marker of cardiac damage from the cytokine storm? Effective treatment will likely be guided by the underlying cause of the elevated hs-TNI levels (eg, interleukin 6 inhibitors for cytokine toxic effects).

Ethnic and racial variation in the US will bring unique challenges for diagnosis, prognosis, and management of COVID-19. The Chinese experience has shown a high comorbidity of hypertension, diabetes, and CVD in patients with COVID-19.[3] Shi et al[1] also noted that prominent comorbidities in those with cardiac injury included hypertension, diabetes, coronary disease, heart failure, and cerebrovascular disease—all more prevalent in African American individuals. African American individuals have higher circulating biomarkers of systemic inflammation and myocyte injury,[4] and subclinical CVD occurs at a young age in African American individuals.[5] Thus, African American individuals may be a particularly vulnerable group in the US to the untoward effects of COVID-19.

Finally, whether cardiac injury as a consequence of COVID-19 infection results in permanent cardiac damage in survivors also remains to be determined. Long-term cardiovascular consequences of COVID-19 will need to be monitored to ensure that this cytokine storm does not bring with it a secondary tsunami wave of cardiovascular events in the future.

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1. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. Published online March 25, 2020. doi:10.1001/jamacardio.2020.0950

2. Jia X, Sun W, Hoogeveen RC, et al. High-sensitivity troponin I and incident coronary events, stroke, heart failure hospitalization, and mortality in the ARIC study. *Circulation*. 2019;139(23):2642-2653. doi:10.1161/CIRCULATIONAHA.118.038772

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. Hackler E III, Lew J, Gore MO, et al. Racial differences in cardiovascular biomarkers in the general population. *J Am Heart Assoc*. 2019;8(18):e012729. doi:10.1161/JAHA.119.012729

5. Lefferts WK, Augustine JA, Spartano NL, Atallah-Yunes NH, Heffernan KS, Gump BB. Racial differences in aortic stiffness in children. *J Pediatr*. 2017;180:62-67. doi:10.1016/j.jpeds.2016.09.071

To the Editor The article by Shi et al[1] studied the clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and associated myocardial injury that was present in almost 20% of cases. The authors should be commended for undertaking the largest analysis so far exploring the association of myocardial injury with mortality in patients with COVID-19. However, one question still remains: what is the cause of myocardial injury in this context? Sepsis, hypoxemia with or without underlying coronary artery disease, and myocarditis have all been proposed.[2] In our view, takotsubo syndrome (TTS) should also be considered in the differential diagnosis of myocardial injury during the COVID-19 pandemic.

After the first reported case in Switzerland on February 25, 2020, the COVID-19 epidemic has spread rapidly in our country, reaching in March the highest cumulative prevalence per inhabitants in the world. The Geneva canton is particularly hit and has decided to centralize all patients with COVID-19 at the University Hospital of Geneva. As of April 3, 2020, 404 patients with confirmed COVID-19 are hospitalized in this center, of whom 62 are intubated in the intensive care unit. Since the beginning of the COVID-19 outbreak, we have noticed an intriguing high number of TTS diagnoses, with an average rate

of 1 case per week instead of a usual approximate rate of 1 case per month.

Takotsubo syndrome, also named broken heart syndrome or stress cardiomyopathy, usually presents like an acute coronary syndrome with chest pain, dyspnea, dynamic changes on electrocardiography, and elevated cardiac biomarkers.[3] Its etiology is not well understood but may be related to coronary microvascular constriction.[4] Obstructive coronary artery disease may occasionally be present concomitantly but is not an underlying cause for TTS. Characteristically, patients show transient left ventricular wall motion abnormalities, of which 4 different patterns can be differentiated.[5] In two-thirds of cases, an emotional or a physical trigger is typically found.[3]

During the COVID-19 pandemic, the huge emotional stress at the population level exacerbated by generalized lockdown and tragic stories involving relatives represent potential triggers of TTS. In addition, severe acute respiratory syndrome coronavirus 2 causes respiratory tract infections, severe pneumonia, sepsis, and hypoxemia, which are also well-known physical triggers of TTS.[3] Therefore, comprehensive cardiovascular examinations, such as electrocardiography, echocardiography, coronary angiography, and cardiac magnetic resonance imaging, should be maintained during the pandemic to better understand the underlying mechanisms of myocardial injury in patients with COVID-19.

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1. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. Published online March 25, 2020. doi:10.1001/jamacardio.2020.0950

2. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. *JAMA Cardiol*. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1105

3. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med*. 2015;373(10):929-938. doi:10.1056/NEJMoa1406761

4. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (part II): diagnostic workup, outcome, and management. *Eur Heart J*. 2018;39(22):2047-2062. doi:10.1093/eurheartj/ehy077

5. Ghadri JR, Cammann VL, Napp LC, et al; International Takotsubo (InterTAK) Registry. Differences in the clinical profile and outcomes of typical and atypical takotsubo syndrome: data from the International Takotsubo Registry. *JAMA Cardiol*. 2016;1(3):335-340. doi:10.1001/jamacardio.2016.0225

In Reply The issue of myocardial damage associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been an important topic from the beginning of the coronavirus disease 2019 (COVID-19) pandemic. Our preliminary investigation demonstrated that myocardial injury is prevalent and associated with worse outcomes in hospitalized patients with COVID-19.[1] With the global outbreak of COVID-19, increasing data focusing on the association of SARS-CoV-2 infection with heart injury have confirmed various pathophysiological hypotheses. The potential mechanisms of myocardial injury in patients with COVID-19, based on our data and evidence from others, include acute myocardial infarction, myocarditis, inflammatory response, acute heart failure, hypoxemia, pulmonary embolism, and even stress cardiomyopathy. These conditions can coexist in the same patients.

Myocardial injury is a common phenomenon in patients with COVID-19, which is the key evidence that SARS-CoV-2 infection can affect the heart. Its prevalence rate was 19.7% in our report of 416 hospitalized patients with COVID-19.[1] Recently, a meta-analysis summarized that at least 8.0% of patients with COVID-19 experienced acute myocardial injury, and the rate was roughly 13-fold higher in patients with severe disease treated in the intensive care unit compared with patients without severe disease.[2]

Various possible pathophysiological mechanisms are widely speculated and gradually confirmed by clinical data. With regard to the cause of myocardial injury, direct viral invasion of the heart similar to pulmonary infection has been hypothesized because angiotensin-converting enzyme 2, proposed as a receptor for SARS-CoV-2, is also extensively expressed in myocardium. Although the first pathological study with limited sample and methodology did not document SARS-CoV-2 infection of cardiomyocytes,[3] it is still a reasonable speculation that direct viral myocardial infection may exist because clinical cases resembling myocarditis have been reported.[4] Systemic inflammatory responses with pneumonia can lead to nonischemic myocardial impairment, especially in the presence of preexisting cardiovascular diseases. Moreover, coronary atherosclerotic plaques with increased inflammatory activity are prone to rupture with subsequent cardiac impairment. A large proportion of myocardial injuries are attributed to type I and II myocardial infarction, defined as thrombosis caused by plaque rupture and caused by the imbalance of myocardial oxygen supply and demand,[5] respectively. This would be caused by the combined effects of inflammation, cardiovascular comorbidities, and other risk factors (eg, older age). There is also the possibility of noncoronary myocardial injury[6] and stress cardiomyopathy, which may be caused by a severe emotional stress and/or physical injury under public health emergencies. The cardiovascular adverse effects of various antiepidemic drugs should also not be ignored.

In conclusion, as the underlying mechanisms of myocardial injury are varied in patients with COVID-19, comprehensive cardiovascular examinations after balancing the risk of infection are crucial for differential diagnosis and precise treatment. In addition to acute myocardial injury, as a larger number of patients are discharged, the long-term cardiovascular consequences of COVID-19 will require further follow-up studies.

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1. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. Published online March 25, 2020. doi:10.1001/jamacardio.2020.0950

2. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109(5):531-538. doi:10.1007/s00392-020-01626-9

3. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420-422. Published correction appears in *Lancet Respir Med*. 2020;8:420-422. doi:10.1016/S2213-2600(20)30076-X

4. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1096

5. Thygesen K, Alpert JS, Jaffe AS, et al; 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). *Circulation*. 2018;138(20):e618-e651. doi:10.1161/CIR.0000000000000617

6. Bangalore S, Sharma A, Slotwiner A, et al. ST-segment elevation in patients with Covid-19—a case series. *N Engl J Med*. Published online April 17, 2020. doi:10.1056/NEJMc2009020

David, Brutus, and Caracalla—A Sculptural Chronology of Anatomical Observation

To the Editor Thanks are due to Gelfman[1] for the reminder that our visual diagnostic skills are not limited to sonography, radiography, and electrocardiography and begin with the real-time observations of intricately dynamic anatomy. I was prompted by his article to look at further works by Michelangelo and noticed that in addition to his description of external jugular distension in Moses, David, and Pietà, Michelangelo's bust of Brutus also demonstrates a dilated right external jugular vein up to the crossing with sternocleidomastoid with the head rotated.

It has been suggested that Michelangelo may have drawn inspiration for this work from the head of a decapitated statue retrieved from the nearby Baths of Caracalla in Rome. This head of Caracalla was reworked as a bust, and a prominent proximal right external jugular vein is visible. Contemporaneous records tantalizingly suggest this bust was, for a time, housed on the same street as Michelangelo's workshop.[2]

The discovery of this already 1300-year-old sculpture fragment in Rome in the mid-1500s postdates the completion of the *David*. However, it is a reminder that we are certainly not the first generation to observe these clinical signs and, thanks to the work of educators such as Gelfman,[1] hopefully also not the last.

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1. Gelfman DM. The David sign. *JAMA Cardiol*. 2020;5(2):124-125. doi:10.1001/jamacardio.2019.4874

2. Bambach CC, Barry CM, Caglioti F, Elam C, Marongiu M, Mussolin M. *Michelangelo: Divine Draftsman & Designer*. The Metropolitan Museum of Art; 2018:187.

In Reply I appreciate the kind words and insightful observations of Breakey in response to "The David Sign"[1] concerning Michelangelo's sculpture, *Brutus* (circa 1542). As Breakey describes, this bust does reveal jugular venous distention (JVD) and is likely based on the sculpture *Caracalla* (circa 212 CE) of the Roman emperor of the same name. This deserves further discussion.

Indeed, JVD has been present in statues that predate Michelangelo's *David* (1504). In my article,[1] I mentioned the presence of JVD in the sculpture *Laocoön and His Sons,* where Laocoön is fighting for his life. This marble sculpture (possibly a copy of an earlier lost bronze work) was created in the Hellenistic period (323 BCE to 31 CE), probably between 42 and 20 BCE (and only rediscovered in 1506). There are other earlier statues from the Hellenistic period that also demonstrate JVD. The bronze *Terme Ruler*, from the third to first century BCE, clearly has JVD. The question I keep wondering is what these artists were trying to portray by emphasizing normal, intermittent JVD. JVD itself wasn't recognized to represent disease until 1728.[2] As a cardiologist in the 21st century, I see the David sign as a recognition of normal, intermittent JVD in excited individuals who are breathing against a partial or completely closed glottis (Valsalva maneuver), such as with grunting respiration, forceful speaking, or heavy labor. As a medical educator, using the methods of visual thinking and the limited understanding of the circulatory system in the past, I see different messages that appear to have evolved over time.

Before William Harvey, MD, the venous system was felt to be a system supplying nutrition to the body from the liver.[3] To my knowledge, the earliest depiction of JVD in Hellenistic statues appears to demonstrate vitality. The *Terme Ruler* is not excited or in battle. He appears vital, standing with an arm holding on to and balancing himself on his spear. The later *Laocoön* is clearly in battle for his life, and his JVD emphasizes his exertion. As noted previously, both the *David* and *Moses* are thought to be in a state of excitement before exertion.[1]

But what about the presence of JVD in *Brutus*? While he is fashioned after the Roman sculpture *Caracalla*, and thus his JVD might represent vitality, according to Wallace,[4] he is different. Wallace describes *Brutus* with "powerful, frowning countenance and the directed gaze…enhanced by the rippling eyebrows…and firmly pressed lips…enhanced by roughened surfaces…a man of principles and action."[4] Thus, *Brutus*' JVD is certainly consistent with Michelangelo's theme of using JVD to represent excitement before action.