comorbidities (hypertension, diabetes, and coronary heart disease), and 13 patients (16%) died from cardiac problems, namely cardiac arrest, acute coronary syndrome (ACS), and malignant arrhythmia (1). Cardiac involvement probably complicates severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients, but the true incidence (considering specific echocardiographic findings) and the attributable mortality are aspects not yet well clarified.

Very few reports have used echocardiographic criteria beyond biomarkers to diagnose cardiac injury, but none have differentiated between myocarditis, cardiomyopathy (stress or septic), ACS, and acute heart failure in the era of COVID-19. Acute cardiac injury was reported in 44.7% of the fatalities in the report by Du and colleagues, but the specific echocardiographic abnormalities are not presented (1). Did these "cardiac injuries" involve patients with myocarditis? Or were there features indicative of stress or even septic cardiomyopathy, mostly reversible entities? Considering biomarkers, troponin levels are markedly increased in myocarditis and ACS. On the contrary, in Takotsubo and septic cardiomyopathy, there is a disparity between biomarker levels and the extent of myocardial dysfunction. In addition, hypoakinesia usually does not correspond to a specific coronary artery territory (2). Therefore, a reference on the nature of cardiac injury would be worthy.

A diagnosis of "cardiac injury" mainly relying on biomarker levels may be misleading. In a recent report involving 416 hospitalized patients from Wuhan, 19.7% presented with "acute myocardial injury." The diagnosis relied on increased cardiac biomarker (hypersensitive troponin I) levels, regardless of the electrocardiographic and echocardiographic findings (3). Du and colleagues presented a high percentage of patients with "cardiac injury"; data on lactate dehydrogenase, creatinine kinase, and aspartate aminotransferase are reported but not on cardiac-specific enzymes (1). On the other hand, cardiac-specific biomarkers alone may not be diagnostic of cardiac damage. TnI is elevated in septic shock, pulmonary embolism, and critically ill patients in ICU. In patients with "cardiac injury," NT-proBNP (N-terminal prohormone of brain natriuretic peptide) levels were found to be elevated (4). However, we have previously found that BNP is a biomarker that correlates with the severity of sepsis (5). BNP may be elevated when patients with SARS-CoV-2 present septic shock resulting from a superinfection, even with normal cardiac function. Additionally, the troponin and BNP levels were normal in a 64-year-old female patient from our ICU, who acutely established pericarditis on the 16th day after COVID-19 diagnosis.

Moreover, in Figure 1C of Du and colleagues, they present a computed tomographic image of a 23-year-old female patient with COVID-19. The cardiac structure seems greatly enlarged; considering the young age of the patient, this finding could correspond to true myocarditis (therefore, ground glass opacities could depict hydrostatic pulmonary edema) (1). It would be informative if the authors provided data on this aspect (increased cardiac dimensions on computed tomographic imaging, a finding beyond the criteria used for "cardiac injury" diagnosis). Inciardi and colleagues reported a 53-year-old woman with COVID-19 who presented acute myopericarditis and cardiogenic shock with severe systolic dysfunction, confirmed with magnetic resonance imaging. Noteworthy, the patient never presented signs of respiratory involvement (6).

Finally, data on the attributable to cardiac injury mortality are totally lacking (1). The proportion of the patients with "cardiac injury" who actually died because of cardiogenic shock is not mentioned. Markers of perfusion, such as low central venous oxygen saturation, would add information on the contribution of cardiac dysfunction to the fatal outcome. Furthermore, did the patients, dying of malignant arrythmia and cardiac arrest, suffer from cardiac comorbidities? Did the arrhythmia occur on a substrate of "myocardial injury," or was this a complication of the prescribed medications (i.e., chloroquine)? All these issues need to be clarified to thoroughly understand the "myocardial damage" that COVID-19 induces. ■

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Reply to Tsolaki and Zakynthinos

From the Authors:

We appreciate the great interest in our paper in the *Journal* entitled "Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study" (1). Some insightful points were raised by Dr. Tsolaki and Dr. Zakynthinos.

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In our study, the lactate dehydrogenase, creatinine kinase, and aspartate aminotransferase levels analyzed were obtained on admission. In an isolation unit, where physical examination is difficult to perform because of donning of protective gear, laboratory findings and chest computed tomographic (CT) scans are crucial tools for disease monitoring and can help identify early risk factors for mortality in patients with coronavirus disease (COVID-19) (1, 2).

The question of how acute cardiac injury should be assessed is debatable. However, according to chapter 2 of the Fourth Universal Definition of Myocardial Infarction published in 2018, "Universal Definitions of Myocardial Injury and Myocardial Infarction," myocardial injury is defined as elevated cardiac troponin values with at least one value above the 99th percentile upper reference limit (3). These are the same criteria used in similar recently published papers on COVID-19 (4, 5). The 44.7% of our patients with acute cardiac injury rely on TnI (troponin I) or TnT (troponin T) measured during patients' hospitalization, whereas other biomarkers, such as CK-MB (creatine kinase MB isoform), NT-proBNP (N-terminal prohormone of brain natriuretic peptide), and BNP, are less sensitive and less specific. Acute cardiac injury was reported in 59% of nonsurvivors in Huang and colleagues' report, which is consistent with our findings (5). It should be clear that cardiac injury is a depictive diagnosis, the spectrum of which ranges from mild injury to myocardial infarction. Various clinical entities may accompany these myocardial abnormalities, such as ventricular tachyarrhythmia, heart failure, kidney disease, hypotension and/or shock, hypoxemia, and anemia (3). Therefore, cardiac injury cannot always be considered as the main driver of death, which is why it was not included in Table 1 of our paper but instead as a complication reflected by TnI or TnT levels as shown in Table 5 of our paper.

The mechanism of cardiac injury in patients with COVID-19 is still unclear. There are several possibilities: *1*) The role of cytokine storm has been previously shown, wherein IL-1β, IL-6, IL-12, IP-10 (IFN-γ–induced protein 10), and MCP-1 (monocyte chemoattractant protein 1) levels are increased in COVID-19 (5, 6). *2*) Oudit and colleagues showed that downregulation of ACE2 (angiotensin-converting enzyme 2) is associated with the degree of macrophage infiltration after myocardial infection. It is speculated that downregulation of ACE2 expression secondary to viral infection may be related to cardiac insufficiency (7). *3*) Long-term bed rest can lead to coagulation system activation, secondary intravascular microthrombosis, and pulmonary embolism. *4*) Hypoxemia, pulmonary vasospasm, inflammation and hypercapnia, and secondary transient pulmonary hypertension can lead to right heart flow limitations. Cardiomyocyte ischemia or hypoxia leads to impaired left heart function and aggravates pulmonary congestion. *5*) Fever, anorexia, and hypoproteinemia can lead to increased pulmonary exudation, rendering the patient vulnerable to secondary infection by other pathogens, inducing multiple organ dysfunction.

Echocardiographic abnormalities observed in patients with COVID-19 included reduced cardiac systolic and diastolic function, stress myocardiopathy, and right heart dysfunction, which can result from right heart volume and/or pressure load related to increased pulmonary resistance, inappropriate mechanical ventilation, or volume overload. However, patients with severe COVID-19 have rapid changes in echocardiographic findings.

Increased cardiac dimension on CT imaging is insufficient to diagnose myocarditis in patients with COVID-19. The standard Dallas pathological criteria for the definition of myocarditis require that an inflammatory cellular infiltrate with or without associated myocyte necrosis be present on conventionally stained heart-tissue sections (8). At present, there has not been autopsy evidence to indicate myocarditis, although a recent study showed the presence of few interstitial mononuclear inflammatory infiltrates. No other substantial myocardial damage has been found in the heart tissue of patients who died of COVID-19 (9).

Figure 1C of our paper is a CT image of a 23-year-old female patient who died of acute respiratory failure. The patient has a very small amount of right pleural effusion, but the CT image of the left lower pulmonary vessels is very clear, which does not show evidence of an increase in vascular pressure. There is no thickening of the blood vessels, and no perivascular exudation is seen. This patient had severe anemia with Hb 44 g/L but no increase in BNP. It is likely that the change in heart shadow seen on CT imaging is caused by anemia.

It should be noted that none of the patients had been on chloroquine, so this could not be the cause of the arrythmias observed in our patients. Perfusion markers such as low central venous oxygen saturation were not available for this study, but we agree that this would be useful information to obtain in future studies.

We thank Tsolaki and Zakynthinos again for their insightful comments. ■

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Calibration Myths in the 2019 American Thoracic Society/European Respiratory Society Spirometry Technical Standards

To the Editor:

Updated American Thoracic Society/European Respiratory Society (ATS/ERS) technical standards for spirometry were recently published in the *Journal* (1). Some recommendations regarding calibration verification are based on expert opinion, not science. Although these recommendations would not cause any harm, they are unproven directives that clinicians will feel obligated to follow. These recommendations are easy to test, overcoming the need to rely on expert opinion. We tested two directives that we believed were particularly dubious.

Use of In-Line Filters

"If an in-line filter is used in spirometry testing, then it must also be used during recalibrations and verifications" (1). The user is not informed as to why a filter must be used during calibration and verifications, but it is presumably related to the potential of the filter to affect flow (i.e., turbulence). However, this is not an issue for volume-based spirometers, which are still in use on some systems. We tested this theory by performing calibration verifications with 3L syringes on several different spirometer types (four pressure differential pneumotachs [two metal screens from different manufacturers; one Fleisch; one Pitot tube], one heated wire pneumotach, and one dry rolling seal volume spirometer) at low, mid, and high flows with and without a filter. The largest difference we measured was ±20 ml (0.7%), well within the 2019 ATS/ERS calibration standard of 3L ± 90 ml (3%) (1). We could not find a clinically meaningful difference in calibration verification results whether a filter was used or not.

Holding the Calibration Syringe

"Holding the syringe body to steady the syringe during a calibration verification can raise its temperature and contribute to measurement error" (1). The theory behind this recommendation is sound: raising the temperature of the gas that is supposed to be measured at room temperature may affect the recorded values. However, can simply holding the calibration syringe affect the temperature of the gas inside the syringe? To test this theory, calibration verification data performed on a pressure differential pneumotach while not holding the syringe was compared with values measured after the syringe was held in a bear hug for a full minute, as well as after the syringe was placed in a heated drier at 96°F for 10 minutes. After the bear hug, the recorded values were +20 ml (+0.7%) at low flows, 0 ml at mid flows, and +10 ml (+0.3%) at high flows. After calibration syringe exposure to 96°F for 10 minutes, the recorded values were +30 ml (+1%) at low flows, 0 ml at mid flows, and +10 ml (+0.3%) at high flows. On the basis of this comparison, holding the syringe during spirometer calibration does not appear to have a significant impact on recorded values. The ATS/ERS recommendations that filters should be used and the syringe not be held during spirometer calibration and verification may not be necessary. ■

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