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Reply to Modesto-Alapont *et al.*

From the Author:

I thank Dr. Modesto-Alapont and colleagues for their thoughtful comments on my editorial (1). They state that mechanical ventilation is ideally instituted on the basis of precise diagnosis and cite one of my chapters. The chapter says the exact opposite. Indeed, they quote a sentence in which Dr. Laghi and I say that physicians do not initiate mechanical ventilation consequent to "slotting a patient into a particular diagnostic pigeonhole." (2)

Dr. Modesto-Alapont and colleagues claim that the Berlin definition enhances the ability to make a precise diagnosis of acute respiratory distress syndrome (ARDS) in patients with coronavirus disease (COVID-19). On the contrary, the question of whether patients with COVID-19 have typical ARDS (or not) is presently much debated. But there is a deeper question. Criteria used in formulating all definitions of ARDS (over the past 32 years) have been chosen arbitrarily with the goal of setting tight boundaries to achieve greater uniformity of patients entered into clinical research studies. None of the definitions of ARDS constitute, in nosological terminology, a "natural kind" (3) on a clinical, etiologic, or even a physiological level. If Pa_{O_2}/FI_{O_2} is 299 on positive end-expiratory pressure 6, the patient has ARDS by the Berlin definition. If, 5 minutes later, body posture is altered and Pa_{O_2}/FI_{O_2} increases to 301, the patient no longer has ARDS. It is imperative that explicit criteria be followed meticulously when entering patients into clinical trials. A wise clinician, however, would believe it daft to switch between diagnostic categories on the basis of a 2-unit difference on a single laboratory test.

Leaving aside the arbitrary nature of ARDS criteria, the diagnosis does not provide justification for a fixed course of action (other than avoiding a V_T of 12 ml/kg). Some patients with ARDS undergo invasive mechanical ventilation, whereas others are sustained with high levels of supplemental oxygen or noninvasive ventilation without ever being intubated (4, 5).

Dr. Modesto-Alapont and colleagues discuss the role of hypothesis and refutation in science. Although they do not state their hypothesis explicitly, it would appear to be along the lines that instituting mechanical ventilation on the basis of a physician's gestalt versus a precise diagnosis results in inferior clinical outcome. They claim that the results of the randomized control trial by the REVA Research Network have tested (and refuted) that hypothesis. Leaving aside that the hypothesis does not possess the characteristics of a good hypothesis (6), especially in terms of parsimony, the data of the REVA trial cannot be used to refute or accept the hypothesis. The focus of the REVA trial was the target for oxygenation during the entire course of mechanical ventilation subsequent to intubation. The results of the REVA trial do not relate to the decision of whether (or not) to intubate a patient. Drawing a parallel between the two is to conflate fundamentally different situations. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Are Patients with COVID-19 Dying of or with Cardiac Injury?

To the Editor:

We read with great interest the paper by Du and colleagues presenting the clinical characteristics of 85 patients in Wuhan dying of coronavirus disease (COVID-19) (1). Around 70% presented

Originally Published in Press as DOI: 10.1164/rccm.202005-1724LE on May 27, 2020

Originally Published in Press as DOI: 10.1164/rccm.202004-1083LE on May 20, 2020

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. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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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.

Originally Published in Press as DOI: 10.1164/rccm.202004-1156LE on May 20, 2020