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EDITORIAL

An international, multicentre survey of echocardiographic abnormalities in COVID-19 patients

Arnold C.T. Ng[1,2], Victoria Delgado[3], and Jeroen J. Bax[3]*

[1]Department of Cardiology, Princess Alexandra Hospital, University of Queensland, Brisbane, Australia; [2]The Faculty of Medicine, South Western Sydney Clinical School, The University of New South Wales, Australia; and [3]Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands

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This editorial refers to 'Global evaluation of echocardiography in patients with COVID-19', by M.R. Dweck *et al.*, pp. 949–958.

Many countries are currently in the throes of the coronavirus disease 2019 (COVID-19) pandemic as their healthcare systems are being tested with the number of sick patients requiring hospitalizations. Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it is increasingly recognized that COVID-19 is associated with increased cardiovascular morbidity and mortality.

There are currently several proposed hypotheses for the positive association between severity of COVID-19 symptoms and higher incidence of adverse cardiovascular outcomes. One possible reason is the higher prevalence of pre-existing cardiovascular disease in elderly patients leading to increased cardiovascular morbidity and mortality. For example, a recent meta-analysis that included 1576 COVID-19 patients from seven studies compared the prevalence of various co-morbidities in patients with severe vs. non-severe COVID-19 symptoms.[1] In the study, severely unwell patients were more likely to have a history of hypertension [odds ratio (OR) 2.36, 95% confidence interval (CI) 1.46–3.83] and underlying cardiovascular disease (OR 3.42, 95% CI 1.88–6.22). However, it was unclear if the underlying cardiovascular co-morbidities directly predispose or cause patients to develop more severe COVID-19 symptoms, or are an innocent bystander where cardiovascular disease is simply more prevalent with advancing age. Another proposed mechanism is that SARS-CoV-2 can directly induce acute myocardial injury via the angiotensin converting enzyme 2- (ACE2) related signalling pathways.[2] It is now known that the SARS-CoV-2 infection is triggered by binding of the viral spike protein to the ACE2 receptor which is highly expressed in the heart and lungs. Finally, SARS-CoV-2 can also cause myocardial injury through a cytokine storm triggered by T-helper cells, and hypoxia from respiratory failure.[3,4] For example, COVID-19 patients who died had a worse proinflammatory profile and higher levels of interleukin-6, D-dimer, ferritin, and lactate dehydrogenase.[5]

Very few clinical studies to date have incorporated imaging analyses to evaluate the extent of myocardial injury in COVID-19 patients, for obvious reasons (e.g. limiting investigations to clinically indicated situations, maintaining social distancing).[6–8] In a small observational study that included 74 COVID-19 patients who underwent clinically indicated echocardiography, 89% of patients had normal or hyperdynamic left ventricular (LV) systolic function, 41% had a dilated right ventricle, and 21% had right ventricular (RV) systolic dysfunction.[6] The number of patients in that study was too small to make any meaningful interpretation on the role of pulmonary dysfunction on RV size and function. In another echocardiography study that included 112 COVID-19 patients, 37.5% had abnormal cardiac troponin levels, 8.9% had abnormal echocardiograms, and 1.8% had abnormal ECG.[7] Of the 14 patients (12.5%) who met the American Heart Association clinical definition of myocarditis based on elevated cardiac troponin levels >3 times the upper limit of normal, and abnormalities on echocardiogram and/or electrocardiogram,[9] six of them had known pre-existing coronary artery disease, heart failure, or acute myocardial infarction. The authors concluded that the abnormal cardiac troponin and echocardiograms/ECGs in those 14 patients were probably secondary to the severity of their systemic illness rather than direct myocardial injury. This is because echocardiography lacks sensitivity and specificity in diagnosing myocarditis compared with the gold standard cardiac magnetic resonance imaging (MRI).[10] Regardless, it is clear that SARS-CoV-2 can directly cause myocarditis, as evidenced by case reports confirming myocarditis on cardiac MRI,[11–14] demonstration of viral particles in endomyocardial biopsies,[15] and detection of SARS-CoV-2 viral RNA in the pericardial fluid.[16]

The study by Dweck and colleagues in this issue of the *European Heart Journal –Cardiovascular Imaging* is the first attempt at an

* Corresponding author. Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. Tel: +31 71 526 2020, Fax: +31 71 526 6809, Email: j.j.bax@lumc.nl

international, large, multicentre survey on echocardiography in COVID-19 patients.[17] All the participating centres, their staff members, and the authors of the study should be respected and congratulated for their work during this difficult period. The clinical indications and echocardiographic findings were prospectively captured in 1216 patients. The majority of the data (73%) were from four countries in Europe (the UK, France, Spain, and Italy in descending order) and the USA. Just over half of the patients (55%) in the study had abnormal echocardiograms, and 15% had severe cardiac disease defined as severe LV or RV dysfunction or cardiac tamponade. Importantly, when patients with pre-existing cardiac disease were excluded, the overall incidence of severe cardiac disease was similar at 13%. Looking from the other side, 44% of all COVID-19 patients had normal echocardiograms, and 54% of patients without pre-existing cardiac disease had normal echocardiograms.

This study is the first to show that the majority of hospitalized COVID-19 patients had abnormal echocardiographic findings, and an abnormal finding was more likely to result in an immediate change in patient management (45% vs. 20%, $P < 0.001$). More severe COVID-19 symptoms, chest pain with ST-elevation, elevated cardiac biomarkers [troponin and brain natriuretic peptide (BNP)], ventricular arrhythmias, and cardiogenic shock were associated with an abnormal echocardiogram on univariable analysis. On the other hand, increased age and moderate/severe COVID-19 symptoms were more likely to be associated with RV abnormality on univariable analysis. Interestingly, the incidence of myocarditis was very low at only 3%. This was consistent with the observation by Deng *et al*., lending weight to the hypothesis that myocardial dysfunction in COVID-19 patients is more likely to be secondary to the severity of the overall systemic illness rather than direct myocardial inflammation.[7] However, this does not definitively rule out SARS-CoV-2-induced myocarditis as no aetiology was provided for the 38% and 25% of patients with LV and RV impairment, respectively. Furthermore, we have already established that echocardiography is not the most accurate diagnostic test for myocarditis.

One significant limitation of the study was the inevitable selection bias by virtue of its design, as already highlighted by the authors. All echocardiograms were performed on a clinical basis, with the majority conducted in intensive care units. As such, the incidence of cardiac abnormalities is likely to be significantly overestimated. Secondly, no follow-up echocardiographic and clinical outcome data were available. Therefore, it is unknown if these cardiac abnormalities are transient or permanent, and their long-term prognostic implications are unclear. In a previous small study that included 123 COVID-19 patients, LV ejection fraction and presence of diabetes were associated with increased mortality on multivariable Cox regression analysis.[8] However, the overall event rate was extremely small (i.e. 16 deaths) and there was a risk of data overfitting in the study. The absence of mortality data in the present large study was clearly a missed opportunity.

Ultimately, the study of Dweck *et al*. raised several important points and questions. First, cardiac abnormalities are very common in COVID-19 patients with severe symptoms. Secondly, the aetiology and natural history of these cardiac abnormalities are unknown. Finally, the long-term implications of these abnormalities in survivors are unknown. As countries continue to be ravaged by the current COVID-19 pandemic and the number of confirmed cases worldwide increases almost exponentially, the present study showed that not only do we need to be vigilant on the acute cardiovascular complications in acutely unwell patients, but we will also probably have to eventually deal with the long-term cardiovascular complications in the ever increasing number of survivors.

Conflict of interest: none declared.

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