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EDITOR'S PAGE


Cardiac Involvement in the COVID-19 Pandemic

Hazy Lessons From Cardiac Imaging?

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Clinical findings in COVID-19 continue to mesmerize clinicians with widely varying presentations that range from asymptomatic and/or mild symptoms to severe illness and mortality. Multiple clinical factors determine prognosis (1,2), but there has been special interest in the presence of cardiac injury, seen in up to 12% of all hospitalized patients, with nearly one-half of the patients referred for cardiac imaging having abnormal studies (3,4). However, the reason why specific individuals may have a propensity for cardiac involvement after SARS-CoV-2 infection remains a mystery, and imaging might provide some lessons. *JACC: Cardiovascular Imaging* (*iJACC*) has seen an excess of COVID-19 papers over the last 6 months, and despite this deluge, only a few of those have contributed to our understanding in a new and novel manner there is so much we still do not know. In this month's issue of *iJACC*, we present a "COVID-19 collection" to share intriguing observations that highlight the multiple, complex diagnostic uncertainties associated with cardiac involvement in patients with COVID-19.

The initial investigations from Wuhan alerted us to the high propensity of hospitalized patients with pre-existing heart conditions to develop cardiac injury (5). The presence of risk factors and pre-existing coronary atherosclerosis, as identified by imaging coronary artery calcification using computerized tomography, was associated with a worse prognosis in hospitalized patients with COVID-19 (6).

Myocardial dysfunction is common in many inflammatory syndromes, and both left ventricular and right ventricular function, especially measured with deformation imaging, has strong prognostic significance in the failing heart (7). The right ventricle has been called the barometer of all that lies ahead (8). Right-heart dilation and dysfunction seems to be a high risk marker for respiratory failure or hospital mortality (9–11). Speckle tracking echocardiography to delineate latent right and left heart dysfunction has improved prognostication of hospitalized patients (11–13). However, most of the prognostic models continue to wrestle with the uncertainties of the risk prediction because of the wide range of underlying mechanisms: from myocardial ischemia due to hypoxia; endothelial dysfunction; atherosclerotic plaque rupture with thrombosis; right ventricular strain due to pulmonary hypertension and embolism; and myocarditis—to stress cardiomyopathy-like presentations. A central question that clinicians continue to ask is whether cardiac imaging could differentiate the different pathophysiological pathways that underlie the development of COVID-19–related cardiac injury. Cardiac magnetic resonance (CMR) can detect multiple pathologies at once (14), including those in patients with COVID-19 (15); techniques like Feature Tracking CMR can provide refined functional information (16) and could be an area of fertile research in these patients.

CMR is now believed to be the gold standard for diagnosing myocarditis (17) because of its high diagnostic accuracy (18). In addition, it can quantitate fibrosis as well as inflammation (19) and identify complex presentations like MINOCA (Myocardial

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Infarction With Nonobstructive Coronary Arteries) or takotsubo that could affect management (20). However, most studies in the published data, except for a few (21), have been small, done at varying times, and are convenience samples. Two studies in this issue of *iJACC* report important findings from the use of CMR imaging for understanding myocarditis-like presentations (22,23). An initial report of 10 cases from Italy described 2 cases of stress cardiomyopathy with apical ballooning, whereas the remaining patients showed diffuse myocardial edema, with only 3 showing the thin rim of sub-epicardial enhancement (22). In the second report of 26 recovered patients who had COVID-19 with cardiac symptoms, abnormalities on CMR were seen in 15 cases, with myocardial edema seen in one-half of the patients and abnormal late myocardial enhancement seen in one-third of the patients (23). Another report of outpatient CMR performed in 16 patients during the post-hospitalization visit revealed late myocardial enhancement with myocardial edema in 3 patients (24). Thus, in patients with COVID-19, despite a high index of suspicion of initial and ongoing myocardial inflammation and/or injury, myocardial necrosis may not be universally seen in all cases with myocarditis-like clinical presentations. Most myocardial histology from autopsy specimens of patients who died of COVID-19 illness have not conclusively established the presence of myocarditis in most of the patients. For example, this issue *iJACC* highlights the story of a 44-year-old patient with COVID-19 who developed transient severe left ventricular dysfunction and third-degree atrioventricular block that required extracorporeal membrane oxygenation support (25). Endomyocardial biopsy samples showed no significant inflammatory infiltrates, and CMR performed at 14 days of recovery showed normalized left ventricular size and function with only diffuse edema without macroscopic necrosis. These data were also consistent with histopathologic assessment presented in an autopsy study of 21 consecutive patients with COVID-19 (26). Lymphocytic infiltrates that suggested myocarditis were seen in only 3 (14%) cases. The autopsy study revealed an increased interstitial macrophage infiltration, a feature that is also seen in other forms of sepsis. All these studies provide some important information, but much remains hazy:

1. We still do not know if there is much classic myocarditis (virus in the myocytes and sufficient acute viral infection-related inflammatory infiltrate that is associated with myocyte necrosis) in these patients with COVID-19.
2. We do not know how frequent reports are from convenience samples; results have been all over the place.
3. Although some papers described an inordinately high degree of CMR abnormalities in recovered patients, it is difficult to be sure that this is all related to classic myocarditis and not due to a number of other things that are happening at the same time.

Thus, the term myocarditis should be used cautiously when describing patients with elevated troponin levels or the presence of myocardial dysfunction in the setting of COVID-19. More work needs to be done to understand the mechanistic underpinnings of myocardial edema or abnormal T1, which could be a cytokine-mediated transient inflammation, edema due to other reasons (e.g., sepsis), and might have different prognostic significance than longer lasting features of myocarditis.

If it is not myocarditis, what else can cause cardiac dysfunction? The SARS-CoV-2 virus infections can create extremely precise and ordered disruptions to the myofibrillar structure and dissolution of the cardiac contractile machinery. A recent study carried out a comprehensive analysis of the cytopathic effects of SARS-CoV-2 on human induced pluripotent stem cells-derived cardiac cell types (27). Cytopathic effects were particularly striking in cardiomyocytes, which manifested a distinctive myofibrillar fragmentation into individual sarcomeres and a loss of nuclear DNA from intact cell bodies. Surprisingly, these cytopathic effects appeared to occur independently of the presence of actively replicating SARS-CoV-2 virus. These data suggest that the direct infection of cardiomyocytes might not be required to elicit cytotoxic cardiac tissue effects. These data might explain why many autopsy specimens have an undetectable virus in the myocardial tissue samples.

When the pandemic first became rampant in March and April 2020, many elective cardiac imaging services were closed, except for emergencies. Specifically, elective procedures with risk of "aerosolizing," such as transesophageal echocardiography (TEE), and the appropriateness of performing TEEs, instead of the strategic use of alternate tests like cardiac computed tomography, were carefully scrutinized (28). However, on several occasions, the reduction in the performance of tests raised questions regarding potential patient care delays, specifically in those with serious cardiac conditions. For example, a multicenter study from Italy recorded a 33% decrease in TEE for infective endocarditis during the COVID-19 pandemic, with an associated doubling of the in-

hospital mortality potentially related to delayed diagnosis of infective endocarditis (29). Moreover, as patients with COVID-19 flooded the hospitals and intensive care units, unique challenges arose that required solutions, inspiring innovative responses. For example, the use of TEE probes to perform transthoracic echocardiography in the prone position for invasively ventilated patients in the intensive care unit highlights one of the several ingenuous approaches used by the cardiac imaging community and their readiness to adapt in the face of new challenges (30). How and when we do imaging might change during and in the aftermath of COVID-19 pandemic (31), and new paradigms will need to consider safety in this new environment in addition to comparative efficacy alone.

Finally, it is essential to mention the wide interest generated by the topic of performing cardiac imaging to identify latent cardiac involvement in patients with COVID-19 (32). Because there are now >7 million COVID-19 cases in the United States, routine cardiac imaging for all would be unrealistic. Moreover, few cardiac imaging studies have addressed the incremental value of cardiac imaging in asymptomatic patients recovered from COVID-19 (21). This might have major implications in allowing participation in regular exercise and affect return to sports for high-level athletes (33,34). We desperately need more information regarding the clinical significance and long-term evolution of imaging findings. Until that time, careful delineation of individual risk with attention to symptoms, biomarkers, electrocardiography, and handheld cardiac ultrasound during clinical evaluations seem justified for rationalizing further use of cardiac imaging. One limitation of the imaging papers on this pandemic is that they often do not, a priori, help us get patient specific, clinically actionable information; most identify damage that has happened, derive prognostic models, or identify general etiologies for abnormal findings like the cause of troponin leak. These studies have not, as yet, helped with creating unique tailored treatment algorithms specific for COVID-19. Because of the uncertainties, it is time we strengthen the evidence. Retrospective cohort and single-center studies are highly unlikely to give us definitive answers to these unknowns. Effort and focus should be concentrated on collating multicenter experience into registries that assess diagnostic strategies while targeting patient-oriented outcomes. If traditional study methodologies fail, new data science approaches may be useful to assess causation and/or effectiveness and risk prediction. As a community, our responsibility is to ensure that our response to the pandemic is based on sound scientific foundations, and this is even more applicable to diagnostic modalities like imaging that can find a lot of incidental pathology in the midst of other relevant findings.

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