The Early COVID-19 Experience:
Interventional Cardiology Fellowship in New Jersey During the Pandemic

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The initial cases of novel Coronavirus (COVID-19) infection occurred in Wuhan, Hubei Province, China in December 2019. Since then, COVID-19 has evolved from an isolated disease in a region of China to a global pandemic that has pushed hospital systems to the brink, brought the world to a standstill and dragged the global economy into a recession. It was originally thought that the novel Coronavirus was primarily a respiratory disorder, but soon it became clear that its impact goes well beyond the lungs, impacting the cardiovascular system, kidneys, brain and other organs, and resulting in severe complications including acute respiratory distress syndrome, cardiogenic shock, systemic thromboembolism and death.

In New York and New Jersey, the early hot spots of the U.S. coronavirus pandemic, hospitals and health systems stepped up in heroic and unprecedented ways to meet the early challenges of the COVID-19 outbreak. As the pandemic started, I was in the middle of my Interventional Cardiology Fellowship training in New Jersey. At our center, many cardiology fellows served on the frontlines of the pandemic. At any given time, a quarter of the fellows were deployed on COVID services, working 12-h shifts as junior attendings on COVID units or as critical care fellows in ICU. This presented the opportunity for fellows to work in a unique multidisciplinary setting that included critical care physicians, pulmonologists, respiratory therapists, neurologists and palliativists, etc. Supportive measures, intubation, ventilator management, proning, resuscitative efforts for cardiopulmonary arrest patients and end-of-life conversations became routine on COVID units. Dire shortages of PPE across the country made acquiring proper PPE difficult and we were instructed to extend the use of our existing PPE and preserve reusable PPE.

Beginning in March 2020, hospital systems nationwide saw a sudden and inexplicable 60-percent reduction in admissions for acute coronary syndromes (ACS). The fear of catching COVID greatly impacted patient behavior with many not seeking medical care despite symptoms of ACS. This has been a universal experience, with similar findings being reported from multiple countries around the world. The volumes in cardiac catheterization labs went down significantly in March and April, and we were wondering, "Where did all the STEMIs go?" As the admission rates for myocardial infarction started to increase again in May and June 2020, we encountered post-MI complications rarely seen in the pre-pandemic period. These complications are typically due to late presentations of myocardial infarctions, and include ventricular septal rupture, papillary muscle rupture and cardiogenic shock due to pump failure.

The patients being admitted with COVID-19 infection at our center were primarily in their 50s and 60s. The most common symptoms at presentation included fever, malaise and shortness of breath. Laboratory abnormalities at presentation included transaminitis, elevated neutrophils, lymphopenia, and elevated levels of CRP, D-dimer, LDH and ferritin. Imaging abnormalities ranged from ground glass opacities to multifocal pneumonia and/ or dense consolidations. (Figure-1)

Many of the worst case of COVID-19 were directly related to cytokine storm, or cytokine release syndrome, an intense inflammatory and immune reaction in which the body releases too many cytokines too quickly into the bloodstream. This rapid release of cytokines in COVID-19 patients was typically catastrophic leading to tachycardia, tachypnea, and a surge in inflammatory markers including D-dimer, CRP, LDH and troponin. At our center, persistent elevations of inflammatory markers correlated directly with a patient's clinical status. Patients with persistently elevated LDH, Ferritin and CRP had worsening infiltrates, worsening hypoxia, increased work of breathing and high-grade fevers. Measurement of inflammatory markers served as surrogate indicators of improvement or worsening in clinical status.

The association between elevated D-dimer levels and hypercoagulability has been demonstrated in COVID patients with resultant arterial and venous thrombosis. This situation sets the stage for some of the most severe thrombotic complications, including acute coronary syndromes, spontaneous occlusions of distal extremities, pulmonary emboli leading to pulmonary hypertension and acute ischemic strokes. Substantial amount of isolated right ventricular involvement and RV failure is seen in COVID patients and is likely attributed to the pulmonary emboli causing right ventricular strain. Left ventricular systolic function remains largely preserved in the absence of biochemical evidence of

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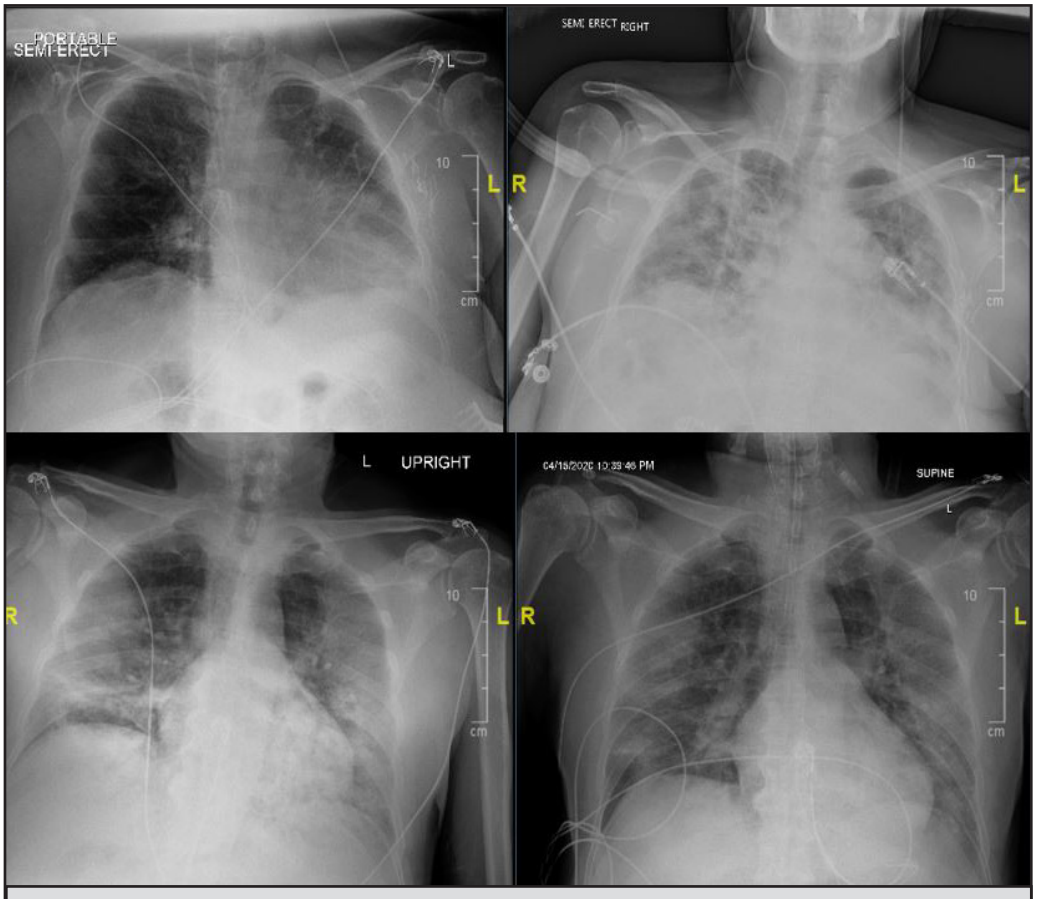

Figure 1: Chest X-ray abnormalities in COVID-19 patients at our center included ground glass opacities, multifocal pneumonia and dense consolidations.

myocardial injury. One of our patients was a 50-year-old female who presented to the ED with a 2-day history of fever and non-productive cough. She was found to have significantly increased work of breathing with severe hypoxia (O2 saturation in 70s) refractory to high flow oxygen therapy, and was intubated shortly thereafter for profound hypoxemia. She was slowly weaned off of oxygen requirements, and successfully extubated on hospital day 6. On hospital day 7, upon rising to go to the bathroom, she became acutely hypoxic and was started on high-flow oxygen and with systemic heparin for presumed thromboembolism. Chest CT showed extensive bilateral pulmonary emboli with right heart strain and extensive parenchymal infiltrates (Figure-2). Within hours of heparin initiation, heart rate decreased and she was able to be weaned off of high flow oxygen. Another 62-year-old male patient with COVID infection and respiratory distress requiring intubation was admitted to the ICU. On hospital day 2, he became acutely hypotensive requiring vasopressor support. 2D echocardiogram demonstrated hyperdynamic LV function with interventricular septal flattening throughout cardiac cycle, and dilated hypokinetic RV with positive McConnell's sign. CT chest showed extensive bilateral pulmonary emboli. Due to unstable hemodynamics, he was given systemic tPA with immediate improvement in HR and BP. His oxygenation and respiratory status improved over the next 24 hours and he was extubated successfully on hospital day 3. He was downgraded out of the ICU to telemetry floor on day 5 and eventually discharged to home on an oral anticoagulant in stable condition.

COVID-19 causes both direct and indirect myocardial injury manifested by elevated levels of circulating troponins, CK-MB and myoglobin. Evidence of myocardial injury in hospitalized COVID patients portends a poor prognosis. Such biomarker elevation is not found to be due to angiographic obstructive epicardial coronary disease in the majority of cases, but rather results from a combination of hypoxia, microvascular thrombosis and vascular inflammation. Increased myocardial oxygen demands in the settings of hypoxia leads to development of supply-demand mismatch and type-II myocardial infarction. Among patients with stable coronary artery disease, acute systemic inflammation in the setting of viral infection can destabilize the previously stable plaque and precipitate acute coronary syndromes. Myocarditis is a relatively rare sequela of COVID infection. It can lead to substantial cardiac damage and severe acute heart failure. It can also evolve into the progressive syndrome of chronic heart failure. Electrocardiograms are usually abnormal in patients with myocarditis. Trans-thoracic echocardiography is an important first line non-invasive test. Cardiac magnetic resonance (CMR) imaging has an integral role in the diagnosis of myocarditis, especially if endomyocardial biopsy is not obtained or cannot be performed.

Shock and multi-organ systems failure are a hallmark of severe COVID-19 infection. Distributive or septic (vasodilatory) shock typically pre-dominates, but many patients are at risk for mixed shock given the propensity for cardiac dysfunction in severe disease. Those with

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underlying heart failure may progress to cardiogenic shock either in isolation or in combination with vasodilatory shock. COVID patients develop severe diffuse pulmonary infiltrates with rapid deterioration to acute respiratory failure. It is usually unknown whether cardiac dysfunction co-exists and to what extent this finding contributes to worsening pulmonary infiltrates and resultant hypoxia. Pulmonary artery catheterization is extremely valuable in such cases for an accurate diagnosis and is usually performed at the bedside. In the setting of refractory hypoxemia and mixed shock, extracorporeal membrane oxygenation (ECMO) should be considered. Dominant configuration in patients with COVID at our center was V-V (veno-venous) ECMO. V-A (veno-arterial) or V-A-V (veno-arterial-venous) ECMO configuration may be considered in selected patients with refractory shock and hypoxemia. Other options for acute mechanical circulatory support for isolated LV failure and shock include Impella and Tandem heart. For patients with isolated right-sided shock and RV failure, early placement of Impella RP is potentially lifesaving.

Patients recovering from COVID illness need careful, close follow-up and vigilance for any unusual symptoms. Some recent studies suggest many COVID-19 survivors experience some type of 'heart damage', even if they didn't have underlying heart disease or were not sick enough to be hospitalized. A study from Germany found that in a cohort of 100 patients recently recovered from COVID-19, cardiac magnetic resonance (CMR) imaging revealed cardiac involvement in 78% of patients and ongoing cardiac inflammation in 60% of patients, which was independent of pre-existing clinical conditions, severity and overall course of acute illness, and the time from the original diagnosis. The most common abnormality was myocardial inflammation (abnormal native T1 and T2 measures) followed by regional scarring and pericardial involvement. At the time of CMR acquisition, these patients were free of symptoms and had negative results on a swab test at the end of their isolation period.

Myocarditis can lead to an increase in ventricular dysfunction and/ or heart failure down the road. There have been some recent reports of young college athletes who have been identified as having 'myocardial injury' following COVID infection. This is a potentially serious issue as asymptomatic (subclinical) or mildly symptomatic myocarditis can lead to similar severe complications as clinically manifest myocarditis does. Cardiac magnetic resonance (CMR) imaging has the potential to identify high-risk patients for adverse outcomes as the CMR evidence of myocardial inflammation has been associated with myocardial dysfunction and death. Evidence based recommendations for return-to-play guidelines are currently limited and subject to change as further data are obtained. Recommendations regarding resumption of intense exercise training requires careful consideration of the severity of prior infection and the likelihood of cardiovascular involvement. The American College of Cardiology (ACC) has urged the research community to perform rigorous well-designed clinical trials to provide a better insight into this subject.

Our understanding of this disease is changing every day and will likely change again in the weeks and months to come. As the second wave of COVID-19 roils the U.S., we need to make sure that patients heed the warning signs of heart attacks and strokes, and act promptly to get to the hospital to seek timely care. Delaying care results in more serious heart damage and even death. The multi-organ and potentially fatal cardiovascular manifestations of novel coronavirus further underscore how important it is for all patients, and particularly those patients with cardiac disease, to take every measure to mitigate the spread of the virus and to protect people at increased risk of severe illness, including social distancing, sanitizing hands and wearing a mask.

References available upon request.

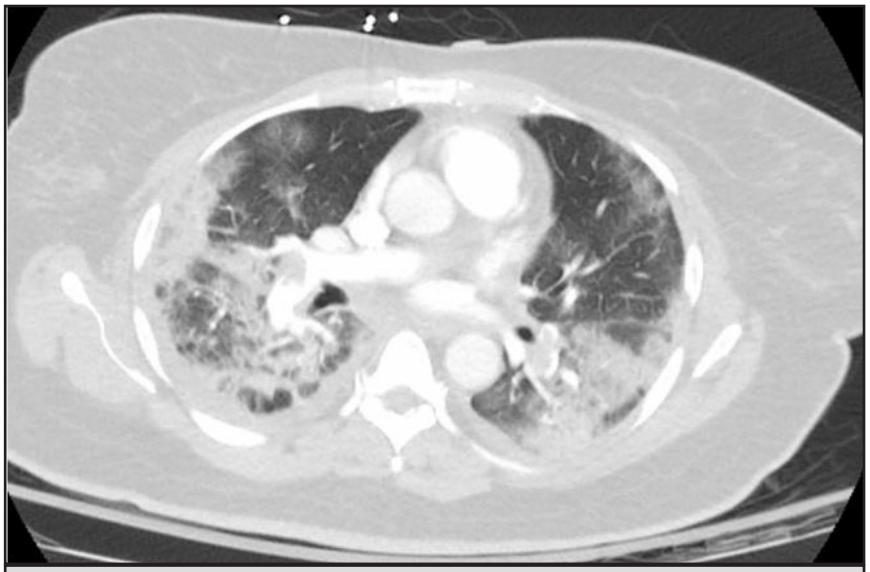

Figure 2: Chest CT scan showing bilateral large pulmonary emboli and extensive pulmonary infiltrates.