COVID-19 Cardiac Injury: An Important Cause of COVID-19 Related Morbidity and Mortality

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Abstract

Coronavirus Disease 2019 (COVID-19) presents as a respiratory illness which can develop into a systemic disease in severely affected individuals. Biomarkers of cardiovascular involvement in patients with COVID-19 include elevated blood levels of D-dimers and cardiac troponin. Clinical evidence of cardiovascular involvement in COVID-19 portents an adverse, and often fatal, outcome. Autopsy studies have elucidated the pathological basis for the clinical manifestations of severe disease. COVID-19 pneumonia has features of an extensive diffuse alveolar damage (DAD) with superimposed thrombotic vasculopathy. Pathological studies have shown a low incidence of lymphocytic myocarditis and the more frequent occurrence of other histopathologic findings including focal cardiomyocyte necrosis, thrombi and megakaryocytes in intramyocardial coronary vessels, and macrophage-dominant interstitial inflammation, in nearly 50% of cases as correlates of the elevated troponin levels. Patients with severe COVID-19 have elevated inflammatory markers including interleukin-6 (IL-6) and C reactive protein (CRP) as well as elevations in von Willebrand factor (VWF) and P-selectin released from perturbed endothelial cells. The systemic endothelial vascular injury likely is a common trigger for both the inflammatory and thrombotic complications of COVID-19. Thus, clinicopathological studies have provided insights and rationale for therapeutic interventions to salvage patients with this terrible disease.

Keywords: COVID-19; Troponin; D-dimer; Coagulopathy; Heart

Introduction

In the last 20 years, three serious coronavirus epidemics have occurred: Severe Acute Respiratory Syndrome (SARS) in 2002, Middle East Respiratory Syndrome (MERS) in 2012, and the Coronavirus Disease 2019 (COVID-19) pandemic beginning in late 2019 and continuing into 2021 [1]. Comparison of the SARS, MERS, and COVID-19 epidemics shows commonalities and unique features of each disease. SARS and MERS affected thousands of individuals in a few countries; whereas, as of August 2021, COVID-19 has affected over 200 million individuals worldwide. Several factors have combined to give rise to the worldwide spread of the COVID-19 pandemic including a high rate of infectivity (reproduction number-R 2.5 or greater) and a longer incubation time with a negative serial interval during which asymptomatic individuals shed virus and can infect others.

COVID-19 infection is initiated by binding of the SARS-CoV-2 virus to a complex of the ACE-2 receptor and accessory proteases, the transmembrane serine protease 2 receptor (TMPR) SS2 and cathepsin L (CTSL), expressed on respiratory epithelial cells in the upper respiratory tract and the lungs of type II pneumocytes, endothelial cells and alveolar macrophages [2]. The distribution of the ACE-2 receptor with the accessory proteases in various cell types in different organs is a determinant of the involvement of these organs in the progression of COVID-19. COVID-19 presents as an acute, febrile, respiratory illness (3). Although many individuals infected with SARS-CoV-2 may be asymptomatic or have mild flu-like symptoms, the respiratory condition can progress to acute respiratory distress syndrome (ARDS), and some individuals can develop a severe illness with multiorgan involvement and severe hyper inflammation [3]. Prognostic indicators of a more serious and potentially fatal course include older age, lymphopenia, elevated D-dimer level, elevated troponin levels, and the co-morbidities of pre-existing cardiovascular disease, hypertension, obesity, diabetes mellitus, and renal disease. Clinical evidence of cardiovascular involvement portends an adverse, and often fatal, outcome [4, 5].

Autopsy studies have been essential for determining the pathological basis for the myriad of symptoms and the mechanisms responsible for multiorgan involvement in severe COVID-19

infection [6]. At our institution, McGovern Medical School, and affiliated hospitals in Houston, obstacles were overcome to keep our autopsy service operational in the early days of the pandemic. This resulted in the publication of one of the first autopsy reports of fatal COVID-19 in the USA [7, 8]. Whereas many institutions closed autopsy services, some other institutions were able to remain operational in early 2020 and contribute observations regarding the pathology of COVID-19 [9]. To date, nearly 70 COVID-19 cases have been performed on our autopsy service. An update on our findings in 34 subjects was presented at recent meetings of the US and Canadian Academy of Pathology (USCAP) and the American Association of Neuropathologists [10, 11]. We have also engaged in reviews of the collective worldwide experience with COVID-19, and a comparative analysis of the pathology of SARS, MERS, and COVID-19 [12, 13]. These publications provide the basis for the observations in this presentation.

COVID-19 respiratory disease has features of extensive diffuse alveolar damage (DAD) with hyaline membranes, type II pneumocyte hyperplasia, low-grade lymphohistiocytic infiltrate, and microvasculopathy with intravascular and extravascular fibrin deposition and intravascular trapping of megakaryocytes, platelets, and neutrophils in capillaries [7-13]. Microthrombi in small pulmonary arteries and pulmonary thromboemboli in segmental pulmonary arteries with pulmonary infarcts and/or hemorrhage are frequently observed (Table 1). In half of the cases, there is super-imposed bacterial pneumonia. Some patients exhibit a variant pattern of acute lung injury known as acute fibrinous and organizing pneumonia (AFOP) characterized by interstitial pneumonitis without hyaline membranes and with intra-alveolar deposits of fibrin enclosed in granulation tissue. The classic DAD and AFOP patterns have subsequently been confirmed in a review of pulmonary pathology in COVID-19 [14].

Pulmonary Parenchyma
Diffuse Alveolar Damage – 90% (31% early, 31% late, 37% mixed)
Interstitial lymphocytic pneumonitis – 10%
Pulmonary Vasculature
Macrothombi – 22%
Microthrombi – 59%
Hemorrhage – 46%
Infarction – 10%
Hypertensive changes – 3%
Pleuritis 6%

Table 1: Pulmonary Findings in Fatal COVID-19 (n=34). Data from: McDonald M, Zhang S, Buja LM, Zhao B. COVID-19 Autopsy Findings: a case series from Houston, TX. Mod Pathol. 2021; 34 (Suppl 2):19-21.

The duration of illness can vary considerably, and in our cases, the clinical course ranged from 24 hours or less to over 12 weeks. The corresponding pulmonary pathology was characterized by the exudative, proliferative, and fibrotic phases of DAD, often with overlapping features of two or three phases in the same lungs. Utilizing IHC with antibodies to viral nucleocapsid protein and spike protein, we have found the detectable virus in type II pneumocytes and endothelial cells only in cases dying with an illness of fewer than two weeks [10]. These findings are consistent with the hypothesis that the initial phase of the illness is driven by a viral infection and the later phase by host response creating an immune-mediated hyperinflammatory state [15, 16].

In addition to major pulmonary pathology, our Houston cases showed subtle changes in the heart consisting of occasional small foci of acute injury of cardiomyocytes without inflammatory cellular infiltrates, and thrombi in intramural coronary arteries as well as focal lymphocytic pericarditis [7, 8, 10, 11]. Large and small infarcts and hemorrhages often were present in the brains. Other changes include depletion of splenic white pulp, focal hepatocellular degeneration, and rare glomerular capillary thrombosis. We concluded that the autopsy findings support the concept that the pathogenesis of severe COVID-19 disease involves initial viral-induced injury of multiple organs, including the heart and lungs, coupled with an intense inflammatory reaction and a prothrombotic coagulopathy.

Our work has been part of a concerted effort by cardiovascular pathologists, individually and through their organizations, the Society for Cardiovascular Pathology (SCVP) and the Association for European Cardiovascular Pathology (AECVP), to obtain and disseminate credible information about the pathological basis for the diverse clinical manifestations of cardiovascular system involvement in COVID-19 [7-11, 17-25].

Early in the pandemic, clinicians noted that hospitalized COVID-19 patients frequently exhibited evidence of cardiovascular as well as respiratory involvement [3-5]. Clinical features of cardiac involvement in COVID-19 included elevated serum troponin levels, arrhythmias, and ST-segment elevations, and/or depression on electrocardiograms pointing to some form of myocardial injury, often in the absence of obstructive coronary artery disease. Another manifestation of cardiac involvement was Takotsubo stress cardiomyopathy or, as it is commonly known, the "broken heart syndrome." The troponin elevations, especially when accompanied by elevations of brain natriuretic peptide (BNP), carried an increased risk for adverse outcomes. Clinicians initially gravitated to myocarditis as a common underlying basis for the clinical findings, and these suspicions were reinforced by certain magnetic resonance imaging (MRI) findings in some patients. However, when autopsy findings began to be collected, initial autopsy findings were largely negative for classical

myocarditis, which is characterized by lymphocytic infiltrates with associated myocyte damage.

To address these discrepancies, a COVID-19 Working Group was established through the leadership of the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology. This COVID-19 Working Group mounted an effort that featured a comprehensive approach to the evaluation of hearts of patients dying with severe COVID-19 [18]. In this international multicenter study, cardiac tissue from the autopsies of 21 consecutive COVID-19 patients was assessed by cardiovascular pathologists (Table 2). The presence of myocarditis, as defined by the presence of multiple foci of inflammation with associated myocyte injury, was determined, and the inflammatory cell composition was analyzed by immunohistochemistry. Other forms of acute myocyte injury and inflammation were also investigated, as well as coronary arterial, endocardial, and pericardial involvement. Lymphocytic myocarditis was present in 3 (14%) of the cases. Increased interstitial macrophage infiltration was present in 18 (86%) of the cases. Mild pericarditis was present in four cases. Acute myocyte injury in the right ventricle, most probably due to strain/overload, was also present in four cases. Epicardial coronary artery lesions were not found. Conclusions of the study were as follows: 1) In SARS-CoV-2 there are increased interstitial macrophages in a majority of the cases and multifocal lymphocytic myocarditis in a small fraction of the cases, and 2) other forms of myocardial injury are also present in these patients.

Myocardium
RV – Cardiomyocyte injury related to RV strain secondary to pulmonary disease – 19%
LV and RV – Spectrum
Small vessel thrombi – 19%
Lymphocytic myocarditis – 14%
Diffuse macrophage infiltration – 86%
Pericardium and Endocardium
Focal pericarditis – 19%
Endocardial thrombosis – 14%

Table 2: Cardiac Pathological Findings in Fatal COVID-19 (n=21). Data from: Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, et al. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. Eur Heart J 2020;41:3827–35.

The finding of Basso and colleagues of a measurable but relatively low frequency of myocarditis has been confirmed by other cardiovascular pathologists based on their case series and two literature reviews of nearly 300 patients [21, 22]. Pathological studies also have shown the more frequent occurrence of other histopathologic findings including focal cardiomyocyte necrosis, thrombi and megakaryocytes in intramyocardial coronary vessels, and macrophage-dominant interstitial inflammation, in nearly 50% of cases. Collectively these changes are more frequent than is lymphocytic myocarditis as correlates of the elevated troponin levels. The pathological correlate of Takotsubo stress cardiomyopathy also was addressed [26].

Various mechanisms for myocardial involvement have been advanced. The presence of virus-like particles has been reported in endothelial and perivascular cells by electron microscopy, raising the possibility of endothelialitis [27]. However, evidence has now been presented that normal vesicular organelles can be misidentified as coronavirus particles [17]. A recent study has shown that the degree of both myocardial macrophage and lymphocyte infiltration correlates with the presence of SARS-CoV-2 infected cells in the interstitium and the duration of disease, but not with underlying medical conditions [24]. Another study has found evidence of viral replication in cardiomyocytes in human-engineered heart tissues [28]. However, other studies have reported limited detection of virus in cardiac endothelial cells and cardiomyocytes in autopsy cases using probes for viral RNA and protein (in situ hybridization and indirect immunofluorescence) [23, 29, 30]. Further work is needed to resolve key issues relating to viral involvement of the myocardium, including the identification of the most commonly infected cell type.

A synthesis of published work to date indicates that myocardial involvement accounting for elevated troponin is multifaceted and may include myocarditis, relatively infrequently, and other types of pathology, collectively more frequently. Importantly, right heart strain secondary to pulmonary disease and hypoxemia also can trigger troponin release [18, 31]. Although overt myocarditis is low, the myocardium in fatal cases frequently is perturbed by interstitial inflammation with increased numbers of activated macrophages. Frequent macrophagic inflammation is a prominent finding in the studies of Basso et al. and confirmed by other groups [18, 19, 22-25]. Fox et al performed a quantitative analysis of this phenomenon and demonstrate a skewed distribution of the number of CD68+ cells in COVID-19 hearts, with upper quantiles showing a significant increase as compared to both matched control hearts, and those with myocarditis [25]. In contrast, hearts from typical inflammatory myocarditis contained increased numbers of CD4+, and CD8+ cells compared to both COVID-19 and control cohorts. Fox et al proposed that the presence of an increased number of CD68+ cells suggests that COVID-19 may incite a form of myocarditis different from typical viral myocarditis.

Fox et al point out that the mononuclear phagocyte system (MPS) is known to be a major contributor to hyperinflammatory and procoagulant secretion syndromes, as demonstrated in the previous SARS epidemic, as well as COVID-19 infection [25]. They postulated that the SARS-CoV-2 virus may elicit a

unique inflammatory response in infected patients that leads to an endothelial injury that can lead to clotting at the arteriole, venule, and capillary level, initiating thrombosis and resulting ischemia/reperfusion injury. An alternative and/or additional consideration is that the presence of endothelial injury could attract non-classical monocytes (i.e., M1) to the site resulting in macrophage-induced activation of the complement pathway, and subsequent apoptotic injury. These considerations are the subject of ongoing investigations.

The early clinical impression of widespread myocarditis was supported by a magnetic resonance (MR) imaging study that reported a high rate of positivity of scans and persistence of positivity in several patients [32]. An important but often overlooked point is that the MRI consensus criteria (Lake Louise criteria) criteria were validated for confirmation of myocarditis in cases with clinical features of myocarditis but were not intended for non-discriminate screening of patients [17]. In retrospect, certain imaging studies were overinterpreted and received sensationalized reporting in the lay press causing alarm that COVID-19 was producing large numbers of individuals with chronically impaired cardiac function ("cardiac cripples") [31]. While as a group, patients who recover from COVID-19 have been reported by some centers to have more abnormalities on MR imaging than control groups, only a small percentage of patients who recover from COVID-19 meet full imaging criteria for myocarditis and show evidence of chronic cardiac dysfunction. Therefore, a conservative approach is imperative in the interpretation of MR studies in individuals recovering from COVID-19 and in decision-making for competitive athletes [17, 31-33]. The reported cardiac pathological changes seen at autopsy likely are limited to severely ill patients with elevated troponin levels.

Recently, the Centers for Disease Control and Prevention has reported a small number of cases of myocarditis and pericarditis in patients in the United States after they received COVID-19 messenger RNA (mRNA) vaccination. The diagnosis of myocarditis was made using diagnostic imaging and laboratory data. Histological documentation has now been reported of myocarditis with mixed inflammatory infiltrates and associated myocyte necrosis in two patients within two weeks of vaccination. This worrisome development needs careful monitoring [34].

Pathological studies have alerted the clinical community that a major feature of COVID-19 is the development of a pro-thrombotic state and that severe COVID-19 is a systemic vascular disease [35, 36]. The autopsy findings of microangiopathy and macroangiopathy pointing to a coagulopathy correlate well with clinical findings in COVID-19. Clinically, severe COVID-19 is characterized by a hypercoagulable state, with venous thrombosis and arterial thrombosis, along with elevated markers such as von Willebrand factor (VWF) and D-dimer

[37-40]. Patients with severe COVID-19 also show clinical signs of systemic inflammation and have elevated inflammatory markers including IL-6 and CRP. They may also show elevations in VWF and P-selectin, which are stored in resting endothelial cells and released from endothelial cells during vascular injury. The combination of high VWF levels, elevated P-selectin levels, vascular thrombosis, and vascular inflammation are indicative of endothelial cell activation vascular injury [41]. The vascular injury likely is a common trigger for both the inflammatory and thrombotic complications of COVID-19.

Further work is needed to address several important questions. Is a direct viral infection of endothelial cells or an indirect host inflammatory response to infection responsible for the activation of endothelial cells? Endothelialitis due to viral infection of endothelial cells initially was advanced as the mechanism of endothelial dysfunction [42, 43]. However, infection of endothelial cells outside the lungs appears to be rare, raising the likelihood of indirect mechanisms for endothelial activation and injury [44]. Second, what are the pathways of endothelial injury that are activated during severe COVID- 19? Third, are the mediators released by injured endothelial cells merely linked to severe COVID-19, or do they play a role in the pathogenesis of COVID-19, and are these mediators' therapeutic targets?

A recent study has found evidence supportive of activated neutrophils rather than cytokine-activated endothelial cells in the pathogenesis of coronary vascular thrombosis [45]. Obviously, additional investigation is needed to sort out the triggering mechanisms of microthrombosis.

Concerted efforts by scientists and physicians have yielded a rapid accumulation of knowledge concerning the pulmonary and extrapulmonary pathology of COVID-19. However, given the many unanswered questions regarding the nature of the virus-host interactions in COVID-19, additional well-designed and well-controlled studies are needed. These studies will be particularly important for elucidating the pulmonary and extrapulmonary pathologies in patients suffering from post-acute sequelae of SARS-CoV-2 infection (PASC) or long COVID [46].

While mysteries related to the COVID19 pandemic will require continued investigation, the spectacular achievement of vaccine development against the SARS-Cov-2 virus has generated much-needed optimism that the pandemic can be brought under control [47-49]. However, this optimism must be tempered by the ongoing challenges of achieving worldwide universal vaccination while the virus continues to mutate leading to the emergence of highly infectious variants, including the currently dominant, delta variant.

Autopsy studies firmly established that severe COVID-19 is a systemic disease and provided support for the important role of vascular involvement with endothelial dysfunction [7-13, 17-25]. Autopsy findings have led to significant improvements in treatment

protocols including the early institution of antithrombotic therapy and administration of corticosteroids. While autopsy studies have been crucially important in understanding the pathobiology of the disease, application of virological and epidemiological methods also have been majorly important in understanding the nature of the pandemic and in devising approaches to controlling it. Autopsy studies will continue to have an important role in elucidating the pathophysiological basis for the continually changing epidemiology and clinical manifestations of the COVID-19 pandemic.

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