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Models for COVID-19 Early Cardiac Pathology Following SARS-CoV-2 Infection

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Objectives: The clinical manifestations of COVID-19 associated cardiac complications are heterogeneous, ranging from asymptomatic to severe symptoms, including arrhythmias and cardiogenic shock. For COVID-19 patients with cardiac sequelae, only a small subset of patients have myocarditis; the pathogenesis of cardiac sequelae caused by SARS-CoV-2 other than microthrombi associated sequelae remains to be determined.

Methods: Retrospective analysis of 71 heart autopsy specimens from COVID-19 and putative COVID-19 in the NIH COVID Digital Pathology Repository.

Results: The most consistent observation was localized myocardial cell death not associated with either myocarditis or microthrombi. Red blood cells were typically absent from capillaries but, when observed, were predominately in linear clusters (stacks) of adjacent cells.

Conclusions: Based on our retrospective analysis, we propose that localized ischemia and subsequent cell death by anoxia contributes to the cardiac pathogenesis in some COVID-19 patients. We propose two new models predicting vasoconstriction of cardiac pericyte cells induced by elevated histamine from hyper-activated mast cells or direct infection. We propose that impeded blood flow and cell death by anoxia are initial steps in the development of SARS-CoV-2 induced cardiac injury in COVID-19 patients independent of microthrombi or myocarditis.

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Introduction

SARS-CoV-2 causing the COVID-19 pandemic is an airborne respiratory virus that directly infects cells expressing the angiotensin-converting enzyme 2 (ACE2) protein. Clinical COVID-19 expression varies widely from asymptomatic to severe (He Guiqing et al., 2020, Hu et al., 2020, Mizumoto et al., 2020, Tian et al., 2020). While individual symptoms vary, fairly consistent disease patterns are observed, including cardiovascular complications such as myocarditis. The clinical manifestations of cardiac complications are heterogeneous, ranging from asymptomatic to severe symptoms, including arrhythmias and cardiogenic shock. For COVID-19 patients with cardiac sequelae, only a small subset of patients have myocarditis (Basso et al., 2020, Bearse et al., 2021); the pathogenesis of cardiac sequelae caused by SARS-CoV-2 remains to be determined.

Clinical observations provide some insights into COVID-19 associated sequelae. Preexisting cardiovascular disease (CVD) is common in COVID-19 patients and associated with unfavorable outcomes (Li et al., 2020); patients with CVD were older (66 vs 52 years) and had a higher mortality rate (16.7% vs 4.7%) than those without CVD (Li et al., 2020). A common cause of COVID-19 associated cardiac sequelae are microthrombi (Rapkiewicz et al., 2020). A meta-analysis of observational studies found 14.1% of 77 317 hospitalized COVID-19 patients had cardiovascular symptoms or complications (angina, arrhythmias, myocardial injury, acute heart failure or myocardial infarction) (Sabatino et al., 2020). A study of 784 COVID-19 patients found arrhythmia in 48% of patients with poor outcome
and 6% in patients without poor outcome (Pranata et al., 2020). A retrospective study of 150 COVID-19 patients found myocardial damage in 18% of fatal cases, of which 14.7% also had circulatory failure (Ruan et al., 2020). Myocarditis has been observed in patients with severe COVID-19 (Bernal-Torres et al., 2020, Beşler and Arslan, 2020, Doyen et al., 2020, Sala et al., 2020). Although cardiac injury is common among infected patients, one study found evidence of myocarditis in only 7.2% of COVID-19 autopsies, with functionally significant cases in <2% of autopsies (Halushka and Vander Heide, 2021). COVID-19–associated cardiac sequela appears like myocarditis without associated infiltration of immune cells or inflammation of the cardiac tissues in the majority of the patients.

Clinical laboratory measurements in COVID-19 patients with cardiac sequela are indicators of ongoing damage and death of cardiomyocytes. In COVID-19 patients, elevated troponin 1 level is a biomarker of cardiac injury (Guo et al., 2020, Nie et al., 2020, Shi et al., 2020). In a study of 309 COVID-19 patients, overall mortality was significantly higher in the patients with elevated troponin 1 (n=116, 37.9% vs 11.4%, odds ratio: 4.45, P<0.001) (Shah et al., 2020). Similarly, a study with serum troponin assessment examined 6247 COVID-19 patients and found 15% had mildly elevated and 14% had severely elevated troponin levels with significantly increased odds of death (odds ratio: 2.06, P<0.001 for mildly elevated and odds ratio: 4.51, P<0.001 for severely elevated) (Majure et al., 2021). A multicenter study in Italy of 614 COVID-19 patients reports that 45% had elevated troponin (T or I) levels associated with increased in-hospital mortality (37% vs 13%, P=0.01) (Lombardi et al., 2020). Elevated troponin levels indicate myocyte cell death. Cardiomyocytes do not express the ACE2 receptor used by the SARS-CoV-2 virus making direct infection of cardiomyocytes unlikely. The pathogenesis of myocyte cell death by SARS-CoV-2 remains unknown.

Evidence of SARS-CoV-2 infection of the heart is limited. A study of autopsies of 21 consecutive COVID-19 patients found lymphocytic myocarditis in 14%, mild pericarditis in 19%, and increased interstitial macrophage infiltrate present in 86% of cases (Basso et al., 2020). Bearse et al. found SARS-CoV-2 infection of macrophages and rare endothelial cells in 30 of 41 (73%) consecutive COVID-19 autopsies with only 4 (9.7%) cases of myocarditis (Bearse et al., 2021). Similarly, in a case report of a 69-year-old patient, Tavazzi et al. found infected macrophages in the heart (Tavazzi et al., 2020). A model for SARS-CoV-2 infecting macrophage via Fc receptor uptake of antibody bound virus has been previously proposed (Ricke, 2021). Understanding cardiac sequela in COVID-19 patients can lead to improved treatments.

Based on our retrospective analysis of heart autopsy specimens from patients with COVID-19 or putative COVID-19 in the NIH COVID Digital Pathology Repository, we propose that COVID-19 associated cardiac pathogenesis is caused by localized ischemia and subsequent cell death by anoxia. We propose two models for the initial steps of cardiac pathogenesis associated with COVID-19. These two models involve cardiac capillary vasoconstriction by activated pericytes.

Methods

Available COVID-19 and putative COVID-19 hematoxylin and eosin (H&E) stained digital cardiac images in the NIH COVID Digital Repository (Hewitt et al., 2020) were manually reviewed. Images from 71 deidentified patients were available, labeled: 1-2, 5, 7-9, 25-35, 37-63, 65-90, and 92.

Results

In this retrospective analysis of 71 NIH COVID Digital Pathology Repository heart autopsy specimens, we observed localized regions of myocytes with degenerate or absent nuclei consistent with individual cell necrosis, without cellular infiltration by immune cells. The majority of cardiac capillaries were devoid of red blood cells. When observed, red blood cells were seen in clusters in short segments of residual intact capillaries.

Discussion

In our retrospective analysis of heart autopsy specimens from patients with COVID-19 or putative COVID-19 in the NIH COVID Digital Pathology Repository (Hewitt et al., 2020), we observed localized regions of myocytes with degenerate or absent nuclei consistent with individual cell necrosis, without evidence of cellular infiltration by immune cells (myocarditis). This pattern of histological evidence illustrates cell distress and death. We propose that the lack of observed immune cells in response to cell death likely results from impeded blood flow to impacted cardiac regions.

We present two new hypotheses for the observed cardiac pathology. The first hypothesis is that some pericytes are activated following histamine release from hyper-activated mast cells (Ricke et al., 2020). This model follows the prediction of COVID-19 being a mast cell disease (Afrin et al., 2020) (Malone et al., 2021) (Theoharides et al., 2021) (Figure 1). We predict the SARS-CoV-1 and SARS-CoV-2 nucleocapsid proteins upregulate COX-2 by binding to the promoter resulting in elevated prostaglandin E2 (PGE2) levels (Tomera et al., 2020; Yan et al., 2006). Elevated levels of PGE2 can cause hyper-activation of mast cells, leading to degranulation and release of inflammatory mediators such as histamine (Moriyama et al., 2014). This hypothesis was previously proposed to occur in COVID-19 patients (Tomera et al., 2020). Moreover, pericytes can react to histamine (Simé et al., 1990) and elevated histamine levels are associated with the contraction of pericytes and endothelial cells (Hamilton et al., 2010; Kelley et al., 1988) resulting in impeded blood flow through capillaries. Constricted pericytes also impede cerebral blood flow leading to ischemic events (Attwell et al., 2016). This model predicts pericyte capillary vasoconstrictions resulting in localized myocyte cell death by anoxia.

The second hypothesis is that pericytes are infected by SARS-CoV-2, resulting in constriction and clamping of the pericyte. This second model proposes that SARS-CoV-2 directly infects pericytes causing vasoconstriction (Figure 1). Pericytes express ACE2 (He et al., 2020; Xu et al., 2021; Zhou et al., 2020; Ziegler et al., 2020). A previously proposed model of cross-linked red blood and endothelial cells by SARS-CoV-2 binding to CD147 protein is also consistent with our histology observations (Scheim, 2020); impeded blood flow and cell death by anoxia is possible from “clumps” of cross-linked red blood cells (Scheim, 2020). Herein, we propose that COVID-19 associated cardiac pathogenesis is initiated by vasoconstriction caused by constricted pericytes leading to impeded blood circulation and myocyte cell death by anoxia.

Both of these models are consistent with SARS-CoV-2 infected macrophages observed in heart autopsies (Bearse et al., 2021, Tavazzi et al., 2020), which result in activated mast cells releasing histamine or infected pericytes. Constricted pericytes impede blood flow through capillaries, with subsequent cell death by anoxia (Ricke et al., 2020). The third model we considered, proposed by David Scheim, is for “clumps” of cross-linked red blood cells impeding blood circulation (Scheim, 2020). The three models, or a combination of two or all three models, are consistent with the observed histological evidence. Impeded blood flow and cell death by anoxia may be the cause of cardiac manifestations and abnormal myocardial measures detected by standardized cardiac magnetic resonance in SARS-CoV-2–infected individuals (Puntmann et al., 2020; Rajpal et al., 2021, Starekova et al., 2021). These models could explain cardiac manifestations in patients recovering from COVID-19. 

M. Fremont-Smith, N. Gherlone, N. Smith et al. International Journal of Infectious Diseases 113 (2021) 331–335
COVID-19; for example, the sudden cardiac death of a 65-year-old woman recovering from mild COVID-19 (Yao et al., 2020).

Based on the observation of cardiac changes in asymptomatic individuals, impeded capillary circulation may be a risk factor for individuals infected by SARS-CoV-2. Hyper-activated mast cells and elevated histamine levels may also contribute to the pathophysiology of COVID-19 induced multisystem inflammatory syndrome in children (MIS-C) and adults (MIS-A) and Kawasaki Disease, which can lead to adverse cardiac sequelae (Ricke et al., 2020).

A set of therapeutic agents targeting the mast cells and cyclooxygenase 2 exhibit efficacy in COVID-19 patients (Blanco et al., 2021, Hogan li et al., 2020, Malone et al., 2021, Samingham et al., 2020). The success of these therapies provides indirect support for our proposed pericyte hypotheses that suggest either hyperActivated mast cells release histamine or SARS-CoV-2 infected pericytes cause vasoconstriction. In an experimental viral myocarditis model, treatment with cetirizine, a histamine H1 receptor antagonist, improved survival, lung congestion, myocardial necrosis, and suppressed expression of pro-inflammatory cytokines (Matsumori et al., 2010). These results suggest that histamine released from mast cells may play a pivotal role in viral cardiac pathogenesis. A retrospective study of patients with chronic heart failure (CHF) revealed treatment with famotidine, a histamine H2 receptor antagonist, improved both cardiac symptoms and ventricular remodeling associated with CHF (Kim et al., 2006). A set of H1 receptor antihistamines, including cetirizine, dexchlorpheniramine, loratadine and ebastine combined with azithromycin, exhibit efficacy in COVID-19 patients (Blanco et al., 2021). High dose famotidine (Janowitz et al., 2020, Malone et al., 2021) also exhibits evidence of efficacy in COVID-19 patients (Chow et al., 2021b, Tomera Kevin et al., 2020, Tomera Kevin M. et al., 2020). Combination therapy to target the H1 receptor on mast cells with Cetirizine and the H2 receptor with famotidine also shows evidence of efficacy in COVID-19 patients (Hogan li et al., 2020). Moreover, treatment with high dose celecoxib to target the upregulated COX-2 enzyme shows evidence of efficacy (Hong et al., 2020) as sole therapy and in combination with high dose famotidine (Chow et al., 2021b, Tomera Kevin et al., 2020, Tomera Kevin M. et al., 2020). Montelukast, a leukotriene receptor antagonist, appears to demonstrate clinical utility in COVID-19 patients (Khan et al., 2021). Aspirin exhibits efficacy in COVID-19 patients (Chow et al., 2021a, Mura et al., 2021, Osborne et al., 2021). While the mode of action in COVID-19 patients is unknown, aspirin is known to stabilize mast cells, target COX-2 and anti-coagulate. In a study of Long COVID patients (n=25), 53.8% with chest pain experienced reduction or resolution of symptoms when treated with histamine receptor H1 antagonists loratadine or fexofenadine and H2 antagonists famotidine or nizatidine (Glynn et al., 2021). The efficacy of these treatments provides potential support for the models proposed. We propose that these treatments likely reduce or minimize cardiac pathology associated with COVID-19.

**Conclusion**

Our retrospective analysis of heart autopsy specimens from patients infected with SARS-CoV-2 showed histopathological evidence of myocyte necrosis without cellular infiltration by immune cells. These observations are consistent with the hypothesis that COVID-19 cardiac pathology is initiated by impeded capillary circulation and associated cell death by anoxia. Thus, SARS-CoV-2 associated cardiac pathology may be reduced or preventable with treatments targeting the histamine pathway that exhibit efficacy in treating COVID-19 patients.

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**Author Contribution**

MF-S, PT, DR, and NS contributed to conception and design. MF-S, PT, and DR contributed to retrospective history review. DR and NG contributed to drafting the manuscript, and all authors to critically revising the manuscript. All authors read and gave final approval to the final manuscript.

**Conflict of Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**Ethical Approval Statement**

Ethical approval was not required because this was a retrospective analysis of publicly available deidentified autopsy images.

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334
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