Circulation

RESEARCH LETTER

Unexpected Features of Cardiac Pathology in COVID-19 Infection

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This Research Letter expands our previous report of 10 hearts[1] by adding an additional 12 hearts (for a total of 22 hearts) from deaths confirmed attributable to coronavirus disease 2019 (COVID-19) infection. We identify key gross and microscopic changes that challenge the notion that typical myocarditis is present in severe acute respiratory syndrome coronavirus 2 infection. We speculate on alternative mechanisms for cardiac injury that should be investigated to provide a better understanding of the cardiac manifestations of COVID-19.

In each case, consent for autopsy was granted by the next of kin. These studies were determined exempt by the institutional review board at LSU Health Sciences Center and Tulane University. Representative sections of the left and right ventricles were submitted for routine histology. All sections were stained with hematoxylin and eosin and examined by an experienced cardiovascular pathologist. A subset of the sections was selected for additional immunostaining for lymphocytes, endothelial cells, and DNA/RNA using CD4, CD8, and CD31 antibodies and DRAQ5 (Bio status)/StrandBrite Green (ATT Bioquest) labeling, respectively.

CLINICAL INFORMATION

Ten male and 12 female patients with COVID-19 (median age, 68.5 years; range, 44–79) were included. Nineteen were Black, 1 was Asian, 1 was Hispanic, and 1 was White: 18 of 22 had a history of treated hypertension, 9 of 22 had obesity class 2 to 3, 11 of 22 had insulin-treated type 2 diabetes mellitus, and 4 of 22 had chronic kidney disease (stages 2 and 3). Two patients had a diagnosis of heart failure, 2 had a history of atrial fibrillation, and 1 each had a history of coronary artery disease or stroke. The hospital stay ranged from 0 to 51 days with a median of 11 days. Eighteen patients were intubated, and all patients died of respiratory failure. Brain natriuretic peptide and cardiac troponin I were measured in 21 of 22 patients during hospitalization. Levels of cardiac troponin I ranged from 0.05 to 62.0 ng/mL (normal≤0.04 ng/mL), but it is important to note that 19 of 21 patients had elevations <1.5 ng/mL. Brain natriuretic peptide levels ranged from 42 to 1466 pg/mL (normal <100 pg/mL), with 8 showing no increase and 13 showing elevations from 106 to 1466 pg/mL. Circulating lymphocytes were low to normal ($1.05\pm0.49\times10^3$/μL; normal=$1.1–5.0\times10^3$/μL), indicating a lymphopenia in our cohort.

GROSS FINDINGS

The hearts ranged in weight from 340 to 1010 g. The most significant finding was severe right ventricular dilatation (defined as a right:left ventricular cavity diameter ratio of ≥1:1) in 9 cases (Figure A). No large pulmonary emboli were identified.

Key Words: COVID-19 ■ dilatation ■ heart failure ■ SARS virus ■ severe acute respiratory syndrome

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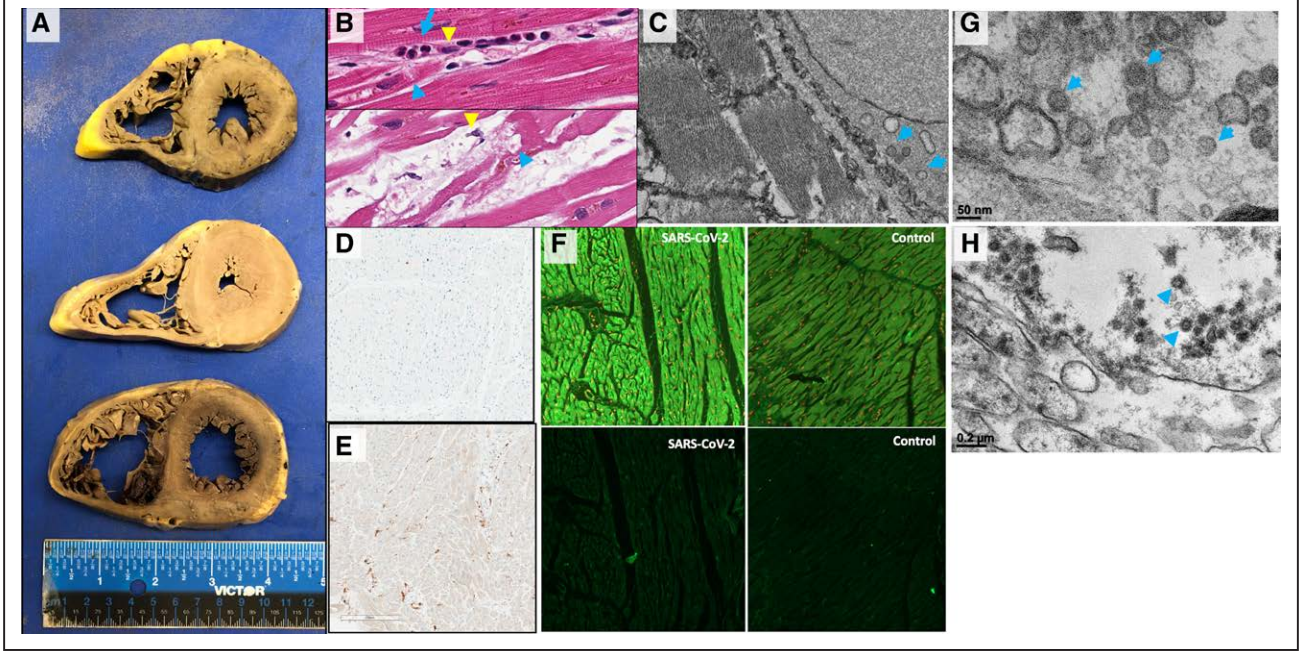

Figure. Cardiac histology.
A, Gross sections demonstrating extensive right ventricular dilatation in 3 hearts (2.9:1.7, 4.0:0.9, and 3.6:3.4 cm); brain natriuretic peptide values in these hearts ranged from 42 to 378 pg/mL. **B**, **Top**, Neutrophils noted in collections within small vessels (blue arrow), plump endothelial cells (yellow arrowhead), and a single perivascular dying myocyte (blue arrowhead). **Bottom**, Single myocyte undergoing degeneration (blue arrowhead) and plump endothelial cell (yellow arrowhead). **C**, Electron microscopy showing particles consistent with SARS-CoV-2 virus present within a cardiac endothelial cell (blue arrowheads) but not present in neighboring cardiac myocytes (left side of image). Six hearts were examined by electron microscopy; subcohort included 3 males/3 females: 5 with hypertension, 3 with insulin-treated type 2 diabetes mellitus, 2 with chronic obstructive pulmonary disease, 2 with a history of atrial fibrillation; heart weight ranged from 420 to 610 g; all cardiac troponin I <0.12 ng/mL. Sparse immunostaining for CD8+ lymphocytes (**D**) and occasional CD4+ lymphocytes (**E**), present mostly in or near small vessels. **F**, **Top**, DNA (DRAQ5)-RNA (StrandBrite Green) staining demonstrates increased intensity of fluorescent staining for RNA with StrandBrite Green under equivalent staining and imaging parameters, in comparison with control myocardium. **Bottom**, Foci of autofluorescence were noted on unstained slides (green) within the 450- to 490-nm range wavelength, possibly representing lipofuscin. Electron microscopy showing particles consistent with SARS-CoV-2 virus present within a pneumocyte (**G**) and similar particles present in renal tubular epithelium (**H**). SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2.

Atherosclerotic narrowing >50% in any vessel was present in only 5 of 22 patients, and no acute coronary thrombi were identified.

MICROSCOPIC FINDINGS

Hematoxylin and eosin-stained sections showed neither large areas of myocyte necrosis, nor significant interstitial lymphocytic infiltrate (Figure B). The sections were remarkable for scattered individual myocyte necrosis (Figure B). Small arterioles, venules, and capillaries contained plump endothelial cells. Immunostaining showed scattered CD4 and CD8 lymphocytes near vascular structures. In rare areas, lymphocytes were seen adjacent to blood vessels, but not surrounding degenerating myocytes. Electron microscopy revealed particles consistent with severe acute respiratory syndrome coronavirus 2 virus in the myocardial endothelial compartment, pneumocytes, and renal tubular epithelium, but not in the myocytes of 6 patients examined by electron microscopy (Figure C, G, and H). By comparison, postmortem analysis of patients who died in the severe acute respiratory syndrome epidemic confirmed viral genome in 35% of the hearts examined.[2]

Elevation of cardiac biomarkers has been widely reported in patients with COVID-19 and has been purported by some to correlate with mortality more directly than other known comorbidities including age, obesity, diabetes mellitus, and chronic lung disease.[3] In our series of 22 patients with COVID-19, the majority of which had mild troponin elevations, there was no pathological evidence of typical lymphocytic myocarditis. Rather, the hearts showed a pattern of individual cell dropout/necrosis/apoptosis not associated with any lymphocytic infiltrate.

The mechanism of cardiac injury in COVID-19 is not known. Our earlier report[1] indicates that our patients experienced diffuse alveolar damage and pulmonary thrombotic and microangiopathic changes. Based on this interpretation and the acute right ventricular dilatation seen in 9 patients, the elevated biomarkers may reflect extreme stress secondary to acute pulmonary disease. Our electron microscopy data showing viral infection of the endothelial compartment are consistent with a recent article by Chen et al,[4] which showed that, despite representing a low absolute number of cells in human hearts, pericytes contain up to 16% of the severe acute respiratory syndrome coronavirus 2–infected cell population and may cause capillary endothelial cell/

microvascular dysfunction, leading to increased thrombosis and individual cell death. The fluorescent RNA data (Figure F) are nonspecific but, coupled with the electron microscopy findings, are suggestive of higher intracellular RNA in vascular endothelium. The effects of the cytokine storm associated with COVID-19 infection, specifically interleukin-6 and interleulin-8, may also play a role in causing platelet activation, neutrophil recruitment and trapping, and corresponding hypercoagulability.[5] Last, given that inflammatory cells can pass through the heart without being present in the tissue proper, a role for cytokine-induced endothelial damage cannot be ruled out.

ARTICLE INFORMATION

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Acknowledgments

The authors are grateful to the families of our patients, the Department of Pathology at LSU Health Sciences Center, Shannon Modia, and Jean Ross for technical assistance in the electron microscopy studies, and to Nicole Bichsel for her invaluable role as autopsy assistant.

Disclosures

None.

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