COVID-19 ACUTE MYOCARDIAL INJURY

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RETROSPECTIVE CLINICAL TRIALS

- COVID-19 primarily effects the upper respiratory tract causing pneumonia, respiratory failure and acute respiratory distress syndrome, there have also been many reports of cardiovascular involvement
  - Retrospective Single Study Trials
    - Huang *et al. Lancet* 2020
    - Chen *et al. Lancet* 2020
    - Wang *et al. JAMA* 2020
  - Retrospective Multi Center Studies
    - Wu *et al. JAMA* 2020
    - Guan *et al. NEJM* 2020
- COVID-19 infection can also present with isolated cardiac symptoms, even in the absence of respiratory symptoms (Inciardi *et al. JAMA Cardiol* 2020)

JAMA Cardiology | Brief Report

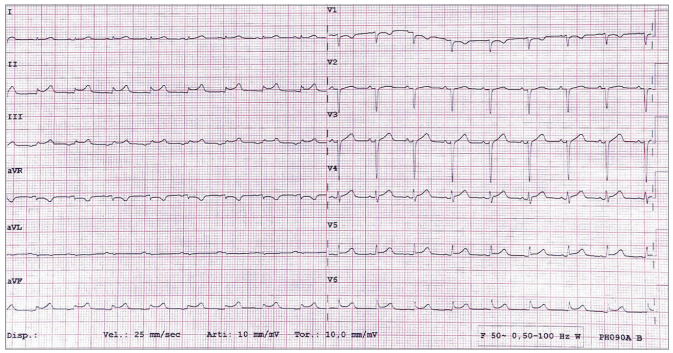
Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19)

Riccardo M. Inciardi, MD; Laura Lupi, MD; Gregorio Zaccone, MD; Leonardo Italia, MD; Michela Raffo, MD; Daniela Tomasoni, MD; Dario S. Cani, MD; Manuel Cerini, MD; Davide Farina, MD; Emanuele Gavazzi, MD; Roberto Maroldi, MD; Marianna Adamo, MD; Enrico Ammirati, MD, PhD; Gianfranco Sinagra, MD; Carlo M. Lombardi, MD; Marco Metra, MD

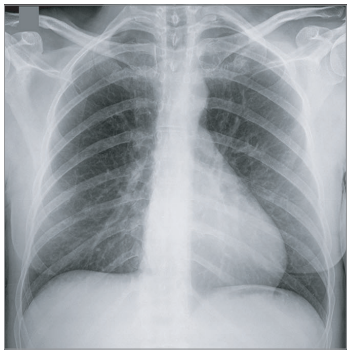
- 53F with no prior medical history presenting to Niguarda Hospital in Milan, Italy in March 2020 with chest pain and dyspnea
- Presenting VS: afebrile, HR 100 bpm, BP 90/50 mmHg, SpO2 98% RA

Figure 1. Electrocardiographic and Chest Radiographic Findings

A Electrocardiography



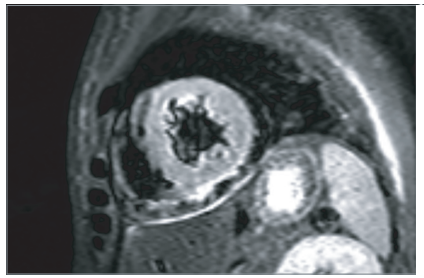
B Chest radiography



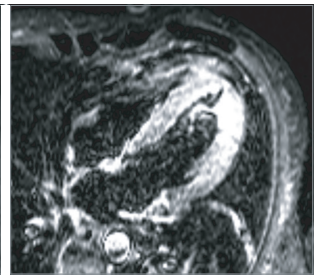
A, Electrocardiography showing sinus rhythm with low voltage in the limb leads, diffuse ST-segment elevation (especially in the inferior and lateral leads), and ST-segment depression with T-wave inversion in leads V1 and aVR. B, Posteroanterior chest radiography at presentation. No thoracic abnormalities were noted.

Figure 2. 1.5-Tesla Cardiac Magnetic Resonance Imaging

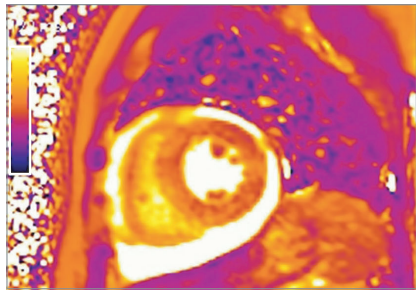
A STIR sequence in short-axis view



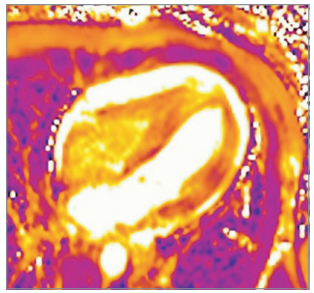
B STIR sequence in 4-chamber view



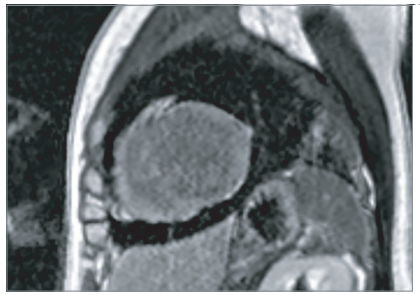
C T2-mapping sequence in short-axis view



D T2-mapping sequence in 4-chamber view



E PSIR sequence in short-axis view



F PSIR sequence in 4-chamber view

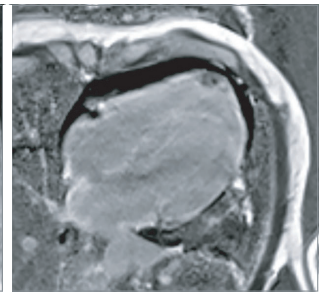


Table. Clinical Laboratory Results

		Result						
Measure	Reference range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Red blood cell count, $\times 10^6$/μL	4.0-5.2	5.5[a]	4.6	4.0[b]	3.9[b]	3.8[b]	3.6[b]	3.7[b]
Hemoglobin, g/dL	12.0-16.0	17.1[a]	14.5	12.4	11.9[b]	12.0	11.4[b]	11.2[b]
Hematocrit, %	37.0-47.0	49.3[a]	42.1	36.0[b]	34.9[b]	35.1[b]	33.9[b]	33.6[b]
White blood cell count, per μL	4000-10 800	8900	12 090[a]	9920	10 900	13 470[a]	13 730[a]	13 500[a]
Lymphocyte count								
Relative, %	20.0-40.0	10.6[b]	NA	NA	NA	NA	NA	7.7[b]
Absolute, per μL	900-4000	950	NA	NA	NA	NA	NA	1040
Platelet count, $\times 10^3$/μL	130-400	152	168	164	213	317	317	360
Sodium, mEq/L	136-145	129[b]	133[b]	129[b]	136	132[b]	134[b]	137
Potassium, mEq/L	3.4-4.5	5.7[a]	6.3[a]	3.9	3.7	3.5	3.6	3.6
Chloride, mEq/L	98-107	89[b]	96[b]	92[b]	92[b]	NA	92[b]	94[b]
Calcium, mg/dL	8.60-10.20	8.63	NA	7.84[b]	8.15[b]	NA	NA	NA
Creatinine, mg/dL	0.60-1.00	0.75	0.76	0.53[b]	0.88	0.99	0.96	0.80
C-reactive protein, mg/dL	<0.5	1.3[a]	0.7[a]	1.0[a]	1.1[a]	0.6	0.4	0.3
Creatine kinase-MB, ng/mL	<4.9	20.3[a]	39.9[a]	30.7[a]	13.3	5.2	3.3	2.8
High-sensitivity troponin T, ng/mL	<0.01	0.24	0.59	0.78	0.89	0.76	0.65[a]	0.63[a]
NT-proBNP, pg/mL	<300[c]	5647	8465	8133	5113	2827	NA	NA

RETROSPECTIVE CLINICAL TRIALS

- Retrospective studies from Wuhan University examining cardiovascular disease in COVID-19 (Guo *et al. JAMA Cardiol* 2020, Shi *et al. JAMA Cardiol* 2020)
  - Patients with baseline cardiovascular disease have increased mortality during COVID-19
    - 7.62% mortality in patients without prior CVD and with normal TnT
    - 13.33% morality in patients WITH prior CVD and with normal TnT
  - Patients who experience acute myocardial injury during COVID-19 infection have worse mortality even in the absence of baseline symptoms (although baseline cardiovascular disease + acute myocardial injury had higher mortality)
    - 37.5% mortality in patients without prior CVD with ELEVATED TnT
    - 69.44% mortality in patients WITH prior CVD and with ELEVATED TnT
  - Acute myocardial injury alone, even without LV dysfunction, was associated with higher mortality, however those with LV dysfunction had the worst mortality of any age group
- Cardiovascular complications of COVID-19 infection are a major contributor to patient mortality, but the pathophysiology underlying this cardiac injury is not presently understood

PROPOSED MECHANISMS OF MYOCARDIAL INJURY

- Type I MI/Plaque Rupture
  - Increased rates of type I MI in influenza (Nguyen *JAMA Cardiol* 2016, Kwong *NEJM* 2018)
- Type II MI/Demand Ischemia
  - Similar to that seen in severe sepsis
- Acute Fulminant Myocarditis
  - Similar to that seen with MERS (Alhogbani *Ann Saudi Med* 2016)
  - Would require viremia and direct infection of myocardium since viral entry is most likely mediated by infection of nasopharyngeal cells, and virus was detected in blood in only a minority of patients (To *Lancet Infect Dis* 2020)
- Cytokine Storm-mediated Injury
  - Autoimmune response to viral infection mediates end-organ damage
  - "Secondary hemophagocytic lymphohistiocytosis"
- ACE2-mediated direct infection of myocardial cells (Oudit *J Clin Invest* 2009, Wrapp *Science* 2020, Patel *Circ Res* 2016)
  - Direct infection of cardiomyocytes
  - Vascular/Endothelial dysfunction
- Limited myocardial tissue pathology has been completed to date

Bonow, Fonarow, O'Gara, Yancy. *JAMA Cardiology* 2020

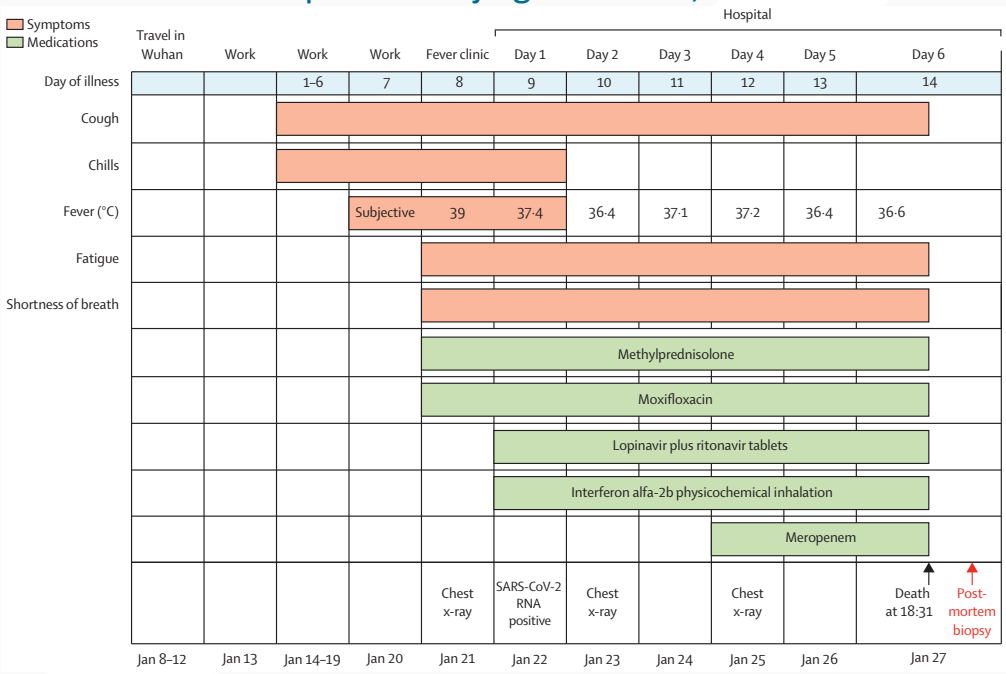
Pathological findings of COVID-19 associated with acute respiratory distress syndrome

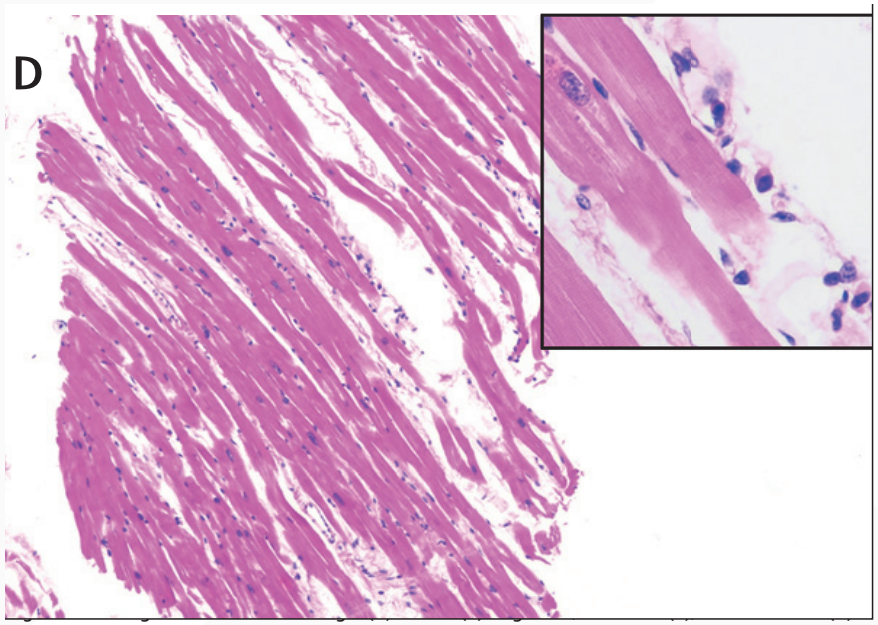
THE LANCET

Feb 17, 2020

Zhe Xu, Lei Shi*, Yijin Wang*, Jiyuan Zhang, Lei Huang, Chao Zhang, Shuhong Liu, Peng Zhao, Hongxia Liu, Li Zhu, Yanhong Tai, Changqing Bai, Tingting Gao, Jinwen Song, Peng Xia, Jinghui Dong, Jingmin Zhao, Fu-Sheng Wang*

- 50 M with history of travel to Wuhan, China January 8-12, admitted to the Fifth Medical Center of PLA General Hospital in Beijing on Jan 21, 2020 with fevers. Unclear PMH





in a patient with severe pneumonia caused by SARS-CoV-2

- 69M presents to ED in Lombardy, Italy with cough, shortness of breath and weakness x 4 days
- CT Thorax with bilateral interstitial infiltrates, labs with leukocytosis and elevated inflammatory markers, ABG with pH 7.2
- TTE with LVEF 35% → 25% within 3 hours
- Cath unremarkable → IABP → worsening hypotension → VA-ECMO + intubation
- Transfer to tertiary MC → EMB performed

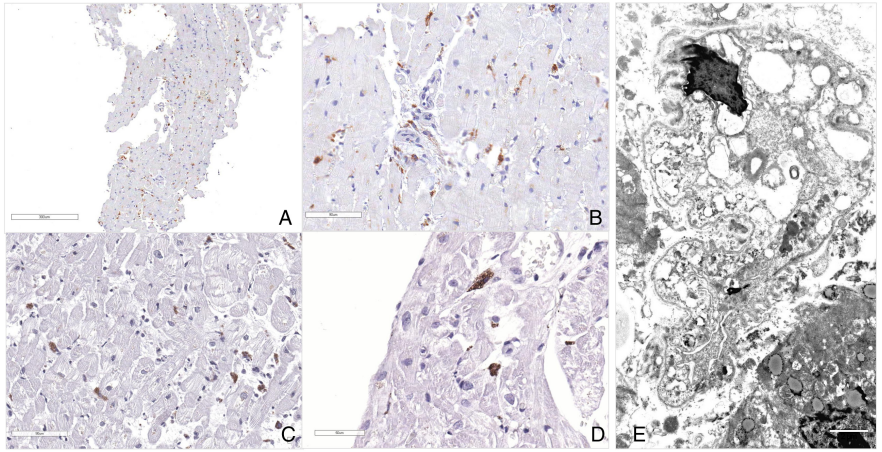


Figure 1 Light microscopy immunostaining of the inflammatory infiltrate. (*A*,*B*) Low- and high-power views of endomyocardial biopsy, with sparse CD45RO positive interstitial cells. (*C*,*D*) Large, vacuolated macrophages immunostained with anti-CD68 antibodies. (*E*) Ultrastructural morphology of a large and cytopathic macrophage. (*A*–*D*: the bar scale is in the left low corner of each panel. *E*: the bar scale is in the right low corner of the panel and corresponds to 2 μm).

Myocardial localization of coronavirus in COVID-19 cardiogenic shock

Guido Tavazzi[1,2], Carlo Pellegrini[1,3], Marco Maurelli[4], Mirko Belliato[2], Fabio Sciutti[2], Andrea Bottazzi[2], Paola Alessandra Sepe[5], Tullia Resasco[5], Rita Camporotondo[6], Raffaele Bruno[1,7], Fausto Baldanti[1,8], Stefania Paolucci[8], Stefano Pelenghi[3], Giorgio Antonio Iotti[1,2], Francesco Mojoli[1,2]*, and Eloisa Arbustini[9]*

ESC European Society of Cardiology

European Journal of Heart Failure (2020)
doi:10.1002/ejhf.1828

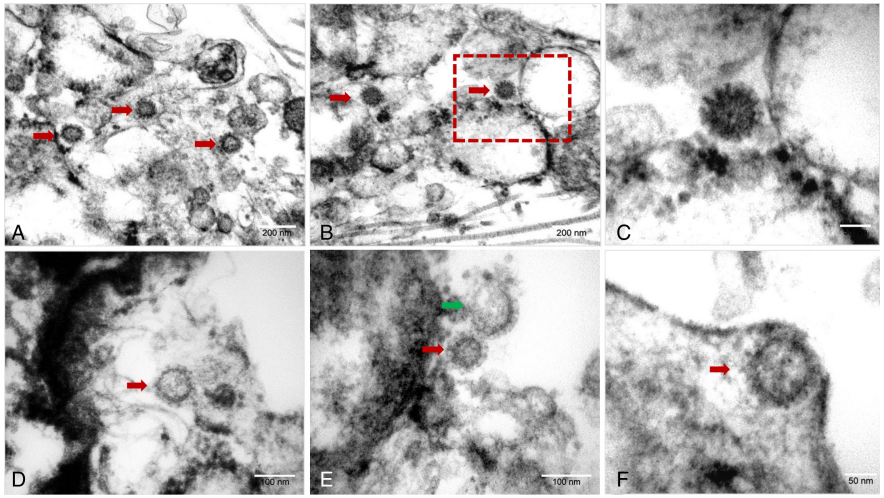
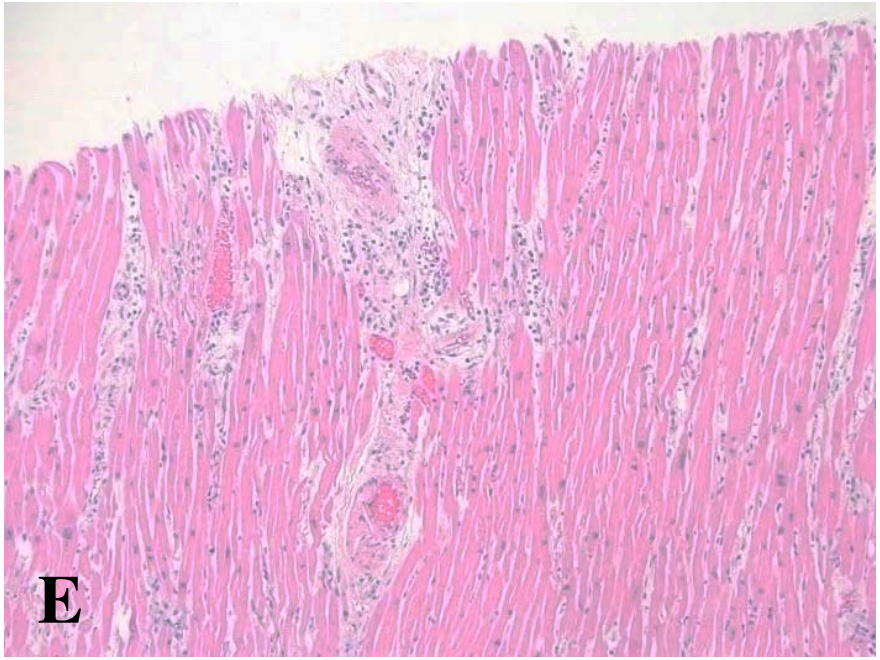


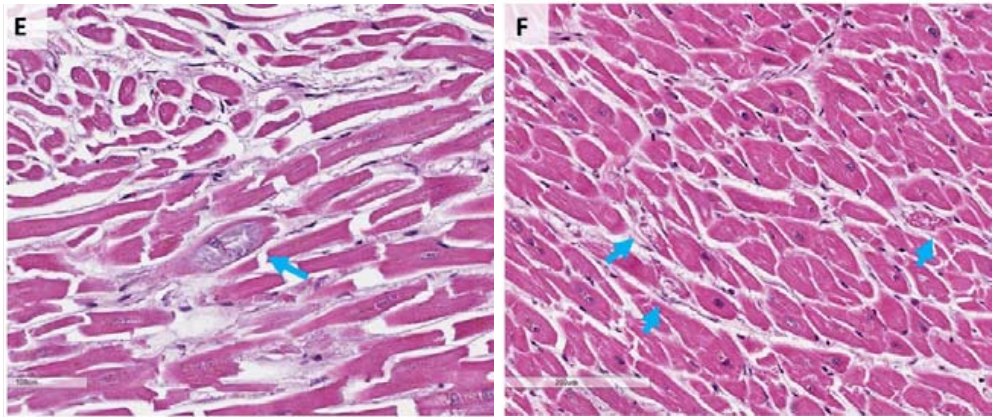
Figure 2 Examples of small groups of viral particles (*A* and *B*; panel *C* shows a higher magnification of one of the viral particles squared in dashed red box of panel *B*) or single particles (*D*–*F*) observed within the interstitial cells of the myocardium of the patient. The red arrows indicate the most typical and easy-to-recognize viral particles, whose size varies from about 70 nm to 120 nm (see the white bars in the panels). Morphology also shows small differences with more or less prominent spikes of the viral crown. The morphology may also show viral particle disruption (*E*, green arrow) or attenuation of spikes of the crown (*D* and *F*), or viral particles in budding attitude (*F*). (Bar scale: *A* and *B*, 200 nm; *C*, 50 nm; *D*, 100 nm; *E*, 100 nm; *F*, 50 nm).

Bradley *et al.* Histopathological and Ultrastructural Findings in COVID-19 Infection
https://www.medrxiv.org/content/10.1101/2020.04.17.20058545v1
Post mortem analysis of 12 fatal cases presenting in Seattle, WA Feb-Mar 2020 (University of Washington)



Heart with lymphocytic myocarditis and myocytolysis
No other details about case were provided

Fox *et al.* Pulmonary and Cardiac Pathology in COVID-19: The First Autopsy Series from New Orleans
https://www.medrxiv.org/content/10.1101/2020.04.06.20050575v1.full.pdf
Post mortem analysis of 4 fatal cases at University Medical Center in New Orleans, LO (LSU/Tulane)



H&E stains of cardiac myocytes with focal degeneration (blue arrows). Myocardium did not show any large or confluent areas of myocyte necrosis but did show scattered individual cell necrosis in each heart examined. They did note some lymphocytes adjacent to (but not surrounding) these individual necrotic myocytes. Possibly early lymphocytic myocarditis

CONCLUSIONS

- Limited myocardial tissue pathology available
- Patient demographics from the autopsy series are limited
- No basic transcriptomic/molecular data available
- Limited cardiac functional data available