Cardiovascular Complications in COVID

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SEPTEMBER 9, 2020

Goals

- COVID and cardiovascular disease pathophysiology – as best we know
- Cardiovascular effects
  - Role of troponin/BNP measurement
  - ACS
  - Thrombosis
  - Heart failure
  - Myocarditis
    - Long-term effects – myocardial fibrosis? JAMA Article, cMRI in recovered patients
- Role of RAAS inhibitors
- Role of statins

- No disclosures

SARS-CoV-2

- Single-stranded RNS coronavirus
- Enters human cells by binding ACE2
  - Highly expressed in lung alveolar cells, cardiac myocytes, and vascular endothelium, and other organs
- As of September 7th, United States:
  - 6,261,216 total cases
  - 188,513 deaths
  - 288,860 cases in the last 7 days
- North Carolina: 10th in the US
  - 177,919 lab confirmed cases
  - 2.897 deaths
  - 765 currently hospitalized

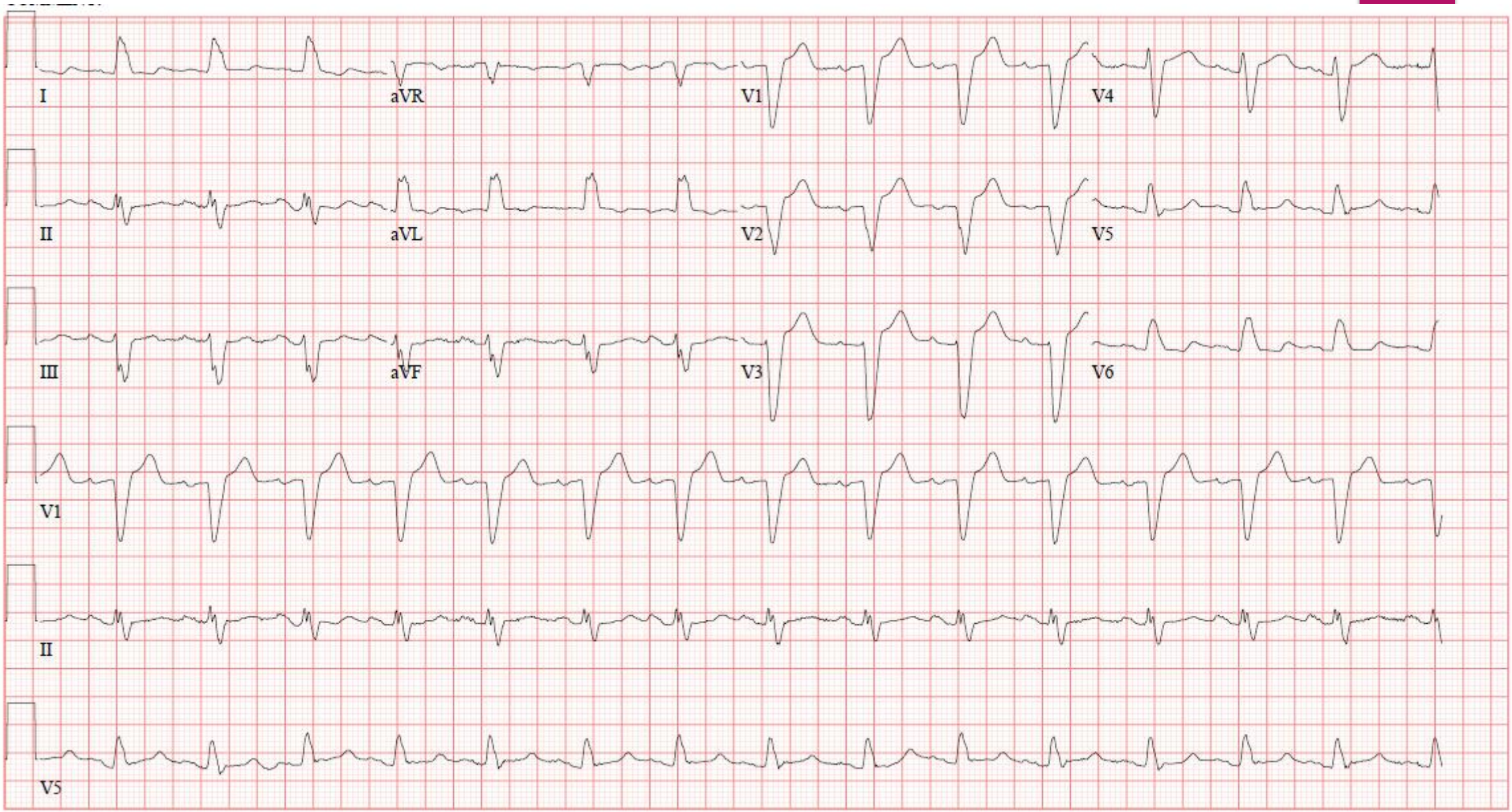
COVID and Cardiovascular Pathophysiology

- SARS-CoV-2 can cause injury to most organ systems
  - 20-30% of hospitalized patients have cardiac injury, up to 55% of patient with preexisting CV disease
- ACE2 is the binding site -for SARS-CoV-2
- Proposed pathophysiology:
  - Inflammatory plaque rupture
  - Stent thrombosis
  - Infection via the ACE2 receptors, causing systemic endothelitis
- Fulminant myocarditis is suspected in 7% of patients with lethal outcome[1]
- Although, no study to date has established a direct mechanism of cardiac cell injury by the virus

1. E. Driggin,*et al.* **Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic**
J Am Coll Cardiol, 75 (2020), pp. 2352-2371

Patient LE

- 78 year-old female presented to the ED feeling poorly, cough, increased shortness of breath, chest tightness for 3 days prior
- Acute on chronic hypoxic respiratory failure on arrival, required high-flow
- PMH: severe COPD, OSA on CPAP, generalized anxiety, tobacco use, hypertension, hyperlipidemia, chronic LBBB, CAD s/p PCI to the LM in 2012 and more recently PCI to the proximal LAD in 2018, and ischemic cardiomyopathy
- Initial Labs: mild renal dysfunction (Cr 1.2). Normal LFTs, troponin 0.06. BNP 285. WBC 18, nl Hgb and Plts
- + COVID
- EKG: NSR with LBBB
- CXR: Diffuse infiltrates throughout both lungs which have developed since the prior study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Patient LE

- Troponin increased to 4.9
- Increasing chest pain and non-productive cough
- Worsening respiratory failure, transitioned to BiPAP overnight

Cardiac Markers in COVID

- Troponin is commonly elevated in COVID patients, poor prognostic sign, although it does not necessary indicate MI or other cardiac injury
- Troponin significantly elevated in more than half the patients that died
- Increased troponin well-established in acute infection, related to inflammation, prothrombotic and procoagulant state
- Rise and fall of troponin is common among patients with acute respiratory infections and correlates with disease severity
- **Only measure troponin if diagnosis of AMI is being considered on clinical grounds**

- BNP is commonly elevated in COVID, but does not necessarily indicate new onset heart failure
  - Elevated in setting of myocardial stress
  - Frequently elevated in severe respiratory illness in the absence of elevated filling pressures
  - Should not necessarily trigger evaluation or treatment for heart failure unless clinically evident
  - Associated with unfavorable outcomes

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Fei Zhou, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao*

Lancet 2020; 395: 1054–62

Cardiac Troponin for Assessment of Myocardial Injury in COVID-19

Journal of the American College of Cardiology
Volume 76, Issue 10, September 2020

Acute Coronary Syndrome

- Theoretical increased risk of acute plaque rupture due to inflammatory response and increased procoagulant and prothrombotic activity
  - Described in influenza infection
- No reported increased in type I MI in COVID patients
- In fact, reduction in STEMI frequency --- although likely due to patient's hesitant to seek care
- Type II MI – due to supply/demand mismatch
  - Need evidence of myocardial injury

Thrombosis

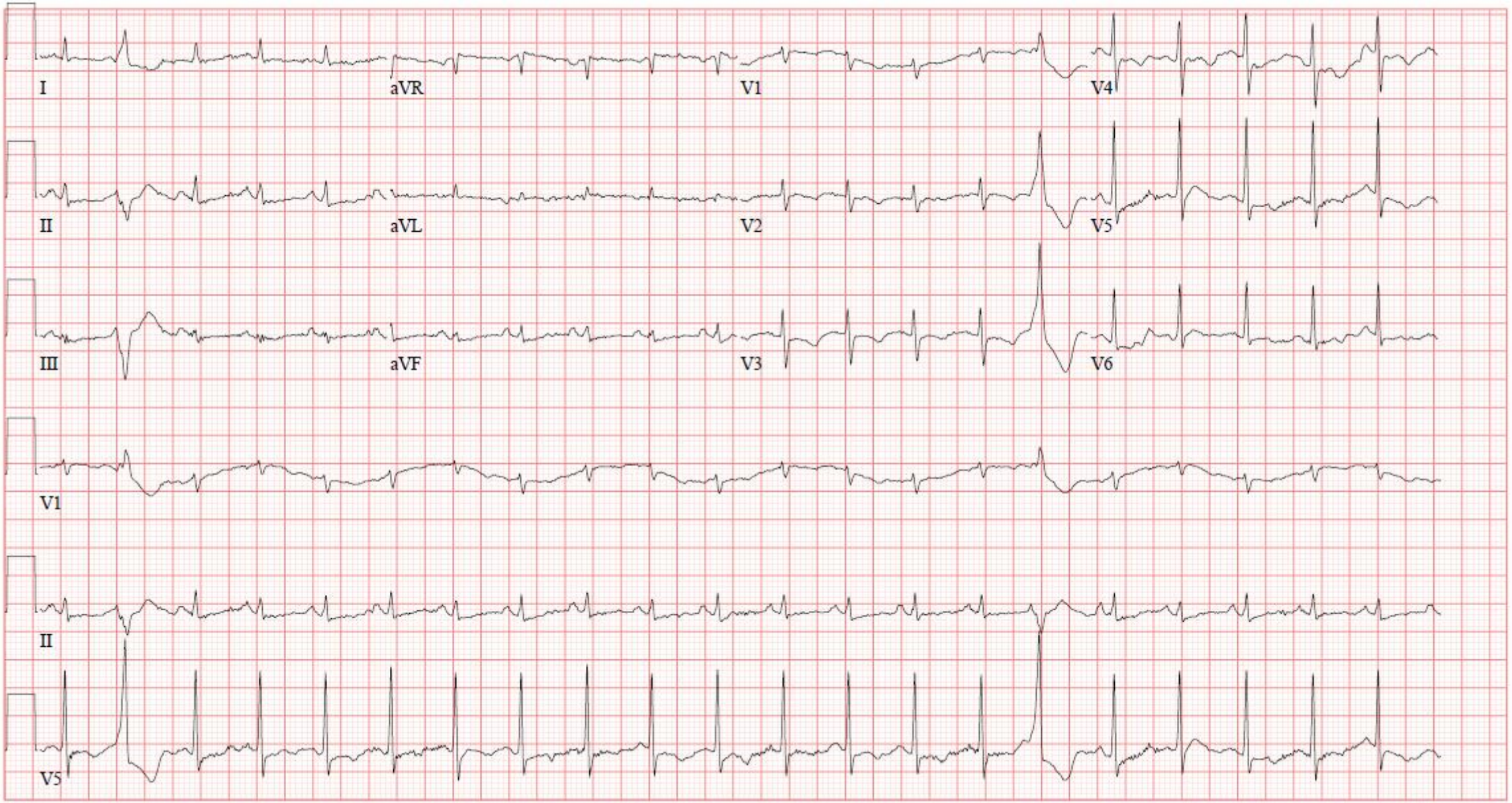
- SARS-CoV-2 activates the coagulation pathway and endothelial dysfunction
- D-Dimer > 1000 ng/mL associated with poor prognosis
- COVID may predispose to arterial and venous thrombosis
- Mechanism not fully understood
  - Cytokine release
  - Critical illness/underlying risk factors/immobility
  - DIC
- ** Many other acute infections or inflammatory diseases associated with increased thrombotic events
- VTE PPX is recommended will hospitalized

- Post-hospital VTE PPX in patients with COVID? [2]
  - Rates of VTE similar for COVID as for all patients with a medical hospital discharge
    - 9/1877 COVID patients with VTE within 42 days of discharge (4.8 per 10000 discharges)
    - 56/18159 (3.1 per 1000 discharges)

1. Bertoletti, L et al. Venous thromboembolism and COIVD-19. Respir Med Res. Apr 2020
2. Roberts, L. et al. Post-discharge venous thromboembolism following hospital admission with COVID. Blood. Aug 2020

Patient MC

- 62 year-old female
- Prior stroke, epilepsy, COPD, depression
- Several family members had recently tested + COVID
- She had presented to the ED 5 days prior to diarrhea and weakness. CT with possible ileus, but infiltrate in lower lobes, concerning for PNA. Normal labs with exception of WBC 16
- Presented back to the ED with hypoxic respiratory failure and altered mental status via EMS.
- Initial lab work: normal BMP, mildly elevated LFTs (ALT 17, AST 44, Alk phos 156, t bili 4.6). Ferritin 14655 . WBC 21.7, Hgb 7.6, Plts 511. INR 1.9 (not on anticoagulation)
- Troponin 0.06. BNP 32
- COVID +
- CT A chest: no PE, mild peripheral bibasilar infiltrates, "not typical appearance of COVID pneumonia"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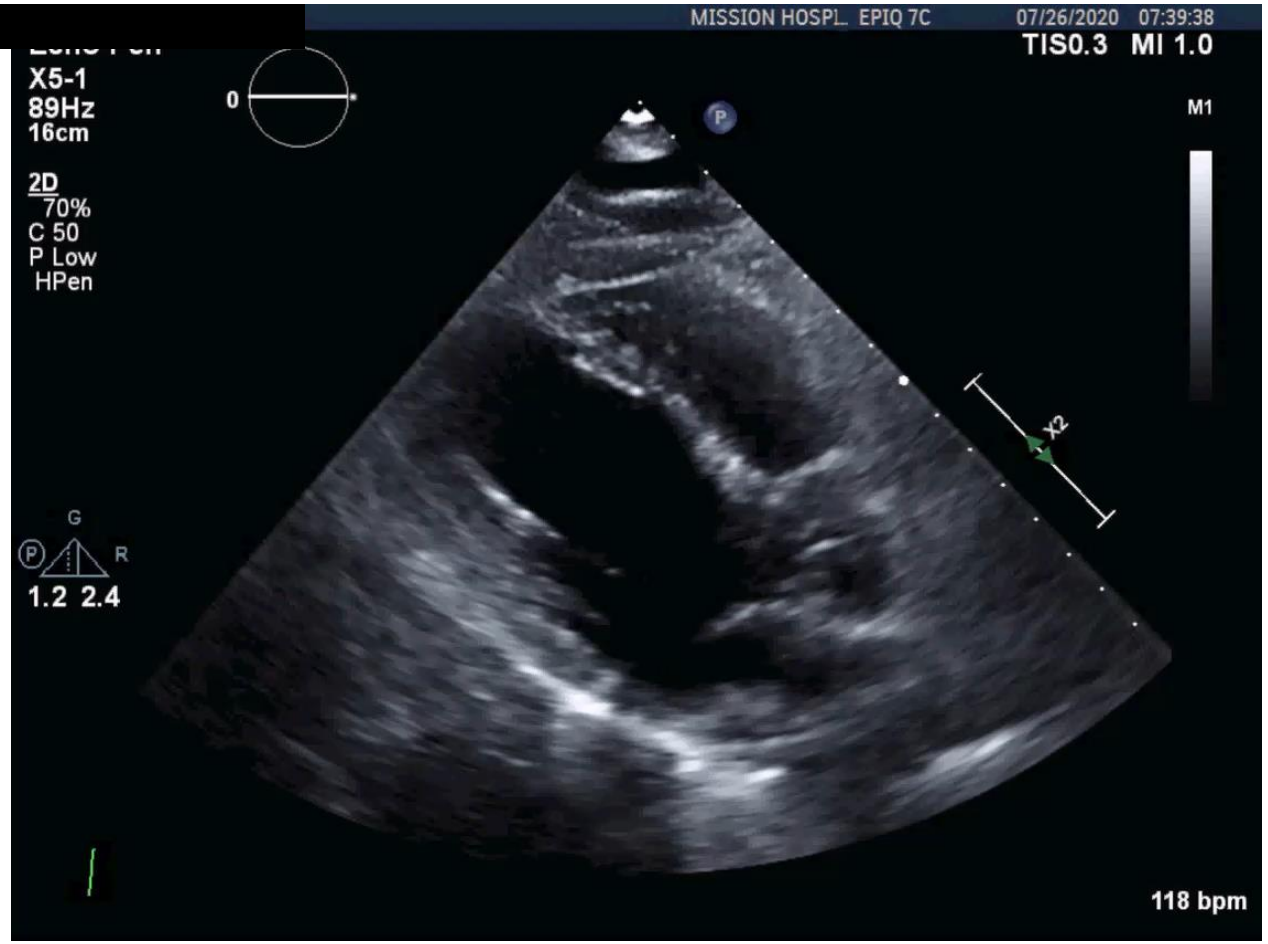
Patient MC

- Rapid deterioration overnight
- Hgb dropped to 4.0
- Worsening respiratory failure, transferred to ICU, intubated
- Shock, with rapidly increasing vasopressor requirements
- Oliguric renal failure
- Negative EGD
- Hematology: "*Her anemia and coagulopathy are very unusual and do not appear to fit into any classic presentations*"
- Echocardiogram the following morning: severe biventricular failure, no significant valvular disease. No pericardial effusion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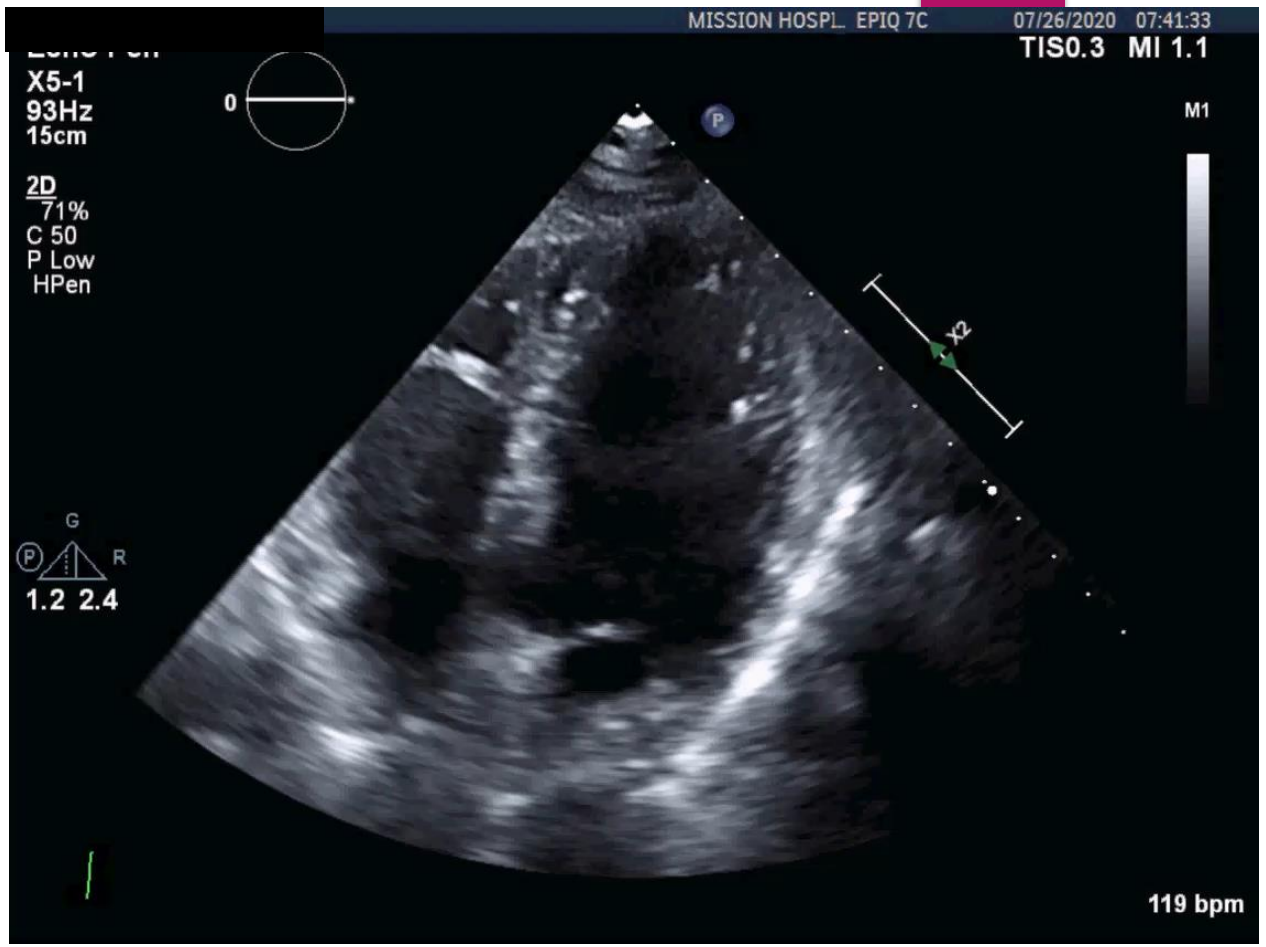
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Cardiomyopathy and Heart Failure

- Cardiac dysfunction is common in patient hospitalized with severe COVID, can be seen in up to 1/3rd of critically ill patients
  - SARS-CoV-2 myocarditis (proposed mechanism due to direct viral infection)
  - Systemic inflammation, cytokine release → Microvascular dysfunction/thrombosis
  - Tachycardia-induced
  - Stress-induced (Takotsubo)
- Management:
  - Mainstay is supportive care, as there is no data to guide optimal management specific to COVID patients with cardiomyopathy
  - Consider PA catheter, for refractory shock
  - Point-of-care echo
  - ECMO?

ECMO Basics

- VV ECMO - oxygenates
- VA ECMO – oxygenates and pumps

ECMO in COVID

- Significant resource utilization
- General consensus: consider in younger patients, minor or no co-morbidities.
  - VA ECMO for refractory shock (SBP < 90 mmHg, CI < 2.2 L/min/m2) while receiving > 0.5 mcg/kg/min norepi or > 20 mcg/kg/min dobutamine
- Absolute contraindications:
  - Advanced age (>60 yo)
  - Severe multiorgan failure (renal failure is not an exclusion)
  - Significant underlying comorbidities
  - Uncontrolled bleeding or contraindications for anticoagulation
  - Inability to accept blood products
  - Severe neurologic injury or advanced dementia
  - Mechanical ventilation > 10 days
  - Ongoing CPR
  - Clinical frailty scale ≥3
- Thrombosis is a major concern, although no data yet

Extracorporeal Life Support Organization (ELOS) Guidelines

VA ECMO in COVID: Outcomes?

- Some propose that VA ECMO can improve outcomes, as it facilitates reduction of IL-6 (increased IL-6 associated with fatal outcomes) by bypassing the lungs – although not proven
- VA ECMO associated with more complications (mainly hemorrhage) compared to VV ECMO
- According to ELOS: 40% predicted survival to discharge on VA ECMO, 58% on VV ECMO – limited data

Myocarditis

- Unclear if there is injury directly from viral infection of the myocardium or indirectly from complications
- Several case reports of acute myocardial inflammation, scant pathologic data
- One post-mortem pathologic study – 50 year-old Chinese male with COVID died from cardiac arrest – significant lung damage, no substantial myocardial damage (outside of few interstitial mononuclear inflammatory infiltrates) [1]
- First direct evidence of myocardial inflammation by endomyocardial biopsy in June – diffuse T-lymphocytic inflammatory infiltrates, edema, focal necrosis. No SARS-CoV-2 genome detected in myocardium [2]
- First report of myocardial localization of SAR-CoV-2 in Italy. 69 year old male with acute respiratory failure, cardiogenic shock. Biopsy with low-grade myocardial inflammation and viral particles in the myocardium. Survived after 5 days on ECMO[3]

1.Xu, Z. et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Me* 2020
2. Sala S. Acute myocarditis presenting as a reverse Takotsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eu Heart. 2020;41

July 27, 2020

Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases

Diana Lindner, PhD[1,2]; Antonia Fitzek, MD[3]; Hanna Bräuninger, MS[1,2]; et al

- 39 autopsy cases of patients with COVID whom pneumonia was the clinical cause of death
- Histopathologic evaluation did not meet criteria for acute myocarditis
- There was evidence of virus present in the heart in 24/39 patients (61.5%)
  - 41% with significant viral load (> 1000 copies per ug RNA)
- Virus was found in the interstitial cells or macrophages infiltrating the tissue and not the myocyte itself.
- Conclusions: Overt myocarditis was not observed in the acute phase, but long term consequences may be an issue…

JAMA Cardiology | Original Investigation

Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

Valentina O. Puntmann, MD, PhD; M. Ludovica Carerj, MD; Imke Wieters, MD; Masia Fahim; Christophe Arendt, MD; Jedrzej Hoffmann, MD; Anastasia Shchendrygina, MD, PhD; Felicitas Escher, MD; Mariuca Vasa-Nicotera, MD; Andreas M. Zeiher, MD; Maria Vehreschild, MD; Eike Nagel, MD

Published online July 27, 2020. Corrected on August 25, 2020.

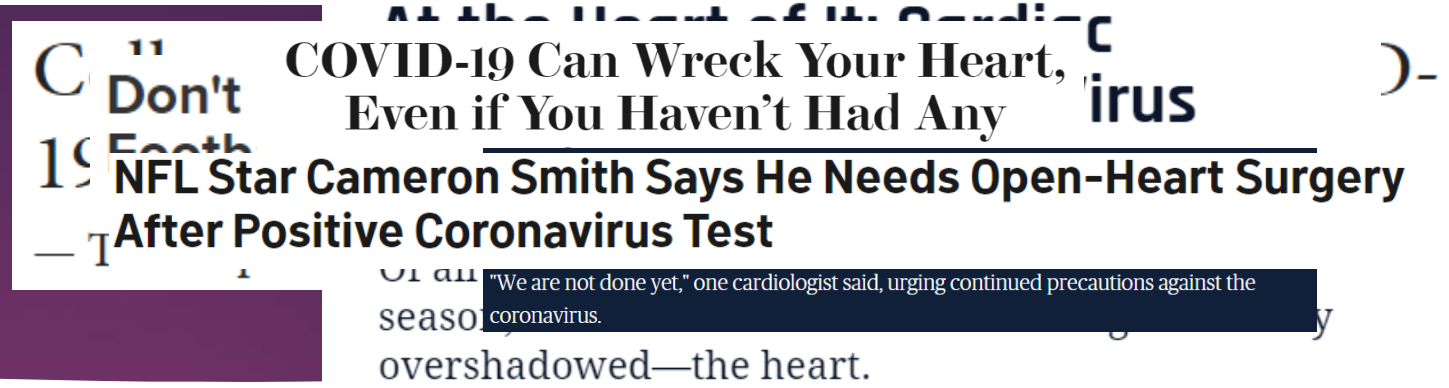
- Evaluate presence of myocardial injury in unselected patients recently recovered from COVID
- 100 patients from University Hospital Frankfurt, between April-June v healthy controls
  - 53% male, average age 49
  - 33% required hospitalization
  - 71 % had elevated high-sensitivity troponin at time of cMRI
- Results:
  - COVID group:
    - Lower LVEF
    - Higher LV volumes
    - Raised native TI and T2
  - 78% had abnormal cMRI findings
    - Raised myocardial native T1 (73)
    - Raised T2 (60)
    - LGE (32)
    - Pericardial involvement (22)
  - Small but significant difference between home v hospital in T1 ($p = 0.008$)
  - Endomyocardial biopsy at in pts with severe findings revealed active lymphocytic inflammation

F, Representative cardiac magnetic resonance images of an adult woman with COVID-19–related perimyocarditis. Panels C and D show significantly raised native T1 and native T2 in myocardial mapping acquisitions. Panels E and F show pericardial effusion and enhancement (yellow arrowheads) and epicardial and intramyocardial enhancement (white arrowheads) in late gadolinium enhancement (LGE) acquisition.

Discussion

- 78% of COVID patients had an cMRI abnormality. The most prevalent abnormality was abnormal T1 and T2 measurements (60%)
  - Increased T1 represents diffuse myocardial fibrosis/edema
  - T2 is specific for edema
  - Increased T1 and T2 = active inflammatory process
  - Increased T1 + normal T2 = usually healed inflammatory process
  - There are many factors that can increase T1 – age, hypertension, diabetes, autoimmune disease
- "Participants with a relative paucity of preexisting cardiovascular conditions and with mostly home-based recovery had frequent cardiac inflammatory involvement. Similar to the hospitalized group"
- "Unlike previous studies, out findings reveal that significant cardiac involvement occurs independently of severity of original presentation and persists beyond the period of acute presentation"

Publicity/Criticism



- Significant media attention, cited as reason to cancel college sports
- 600,000+ views, Altmetric score 10,000
- Numbers in initial results table are mathematically impossible, raising concern about integrity of the data as a whole
  - Interquartile ranges were incorrect
  - Revised data – number of controls with abnormal T1 findings doubled
  - Table 1 p values were correlating COVID patient with healthy controls, not with risk factor-matched controls – many endpoints would no longer be significant
- Correction letter published 8/25/20 "errors in statistical numbers and data" although they state the conclusions still stand
- Many argue that some of the differences on cMRI are caused by the risk factors, not by COVID
- There are likely cMRI abnormalities after many viral infections.
- Did not correlate with clinical myocarditis

RAAS inhibition in COVID

- BRACE CORONA Trial, presented at ECS Congress last week
- Suspending ACE/ARBs did not show clinical benefit in patients hospitalized with mild-to-severe COVID
- 659 patients chronically using ACE or ARBs from 29 sites in Brazil
  - Patients using >3 antihypertensives, Entresto, or hemodynamically unstable at presentation were excluded
- Primary endpoint: # of days alive and out of the hospital at 30 days

- Results:
  - Average number of days alive and out of the hospital was 21.9 for patients who stopped ACE/ARBs compared to 22.9 days for those who continued meds (p = 0.09)
  - Patients alive and out of hospital by the end of 30 days 91.8% in suspended group v 95% in continued group
  - 30-day mortality: 2.7% in suspended group v 2.8% in continued

Conclusions: Continue ACE/ARB and likely ARNI if hemodynamically stable

Statins in COVID

- Some observational studies suggest that statin therapy is associated with reduction in various CV outcomes among hospitalized patients with influenza and/or pna given anti-inflammatory effects
- Currently, no RCT or observational evidence to support starting statins as part of treatment of acute viral illnesses
- Importantly, statins do not appear to be harmful
- Current guidelines advise continuing statins, unless concern for severe rhabdomyolysis

Patient LE

- Chest pain, shortness of breath, worsening hypoxic respiratory failure
- Exam: Appeared in moderate distress. Tachypneic, bibasilar crackles. Tachycardic, no significant murmurs. No JVD. No peripheral edema
- On further discussion, chest pain occurred with coughing
- Recommended against further cardiac evaluation, her clinical presentation consistent with severe COVID pna and type II MI
- Treated with heparin gtt, dexamethasone, convalescent plasma, and remdesivir
- Never required intubation
- Discharged 11 days later back to Givens on home O2

Patient MC

- Refractory mixed shock
- Initial stabilized with addition of dobutamine
- Started on CRRT
- Not a candidate for ECMO given anemia and coagulopathy
- Passed away on hospital day 4

Conclusions

- Like many viral illness, SARS-CoV-2, likely attributes to significant cardiovascular complications, which are associated with poorer outcomes
- The full scope of cardiovascular involvement is not fully realized, although a lot of preliminary data from small studies raising concern for significant morbidity