Dr. Rhee is a general cardiologist with specialized clinical and research training in cardiovascular drug toxicity and pharmacogenomics. She completed clinical cardiology fellowship and internal medicine residency training at Stanford University School of Medicine. During her post-doctoral training, Dr. Rhee's research focused on elucidating cardiotoxic effects of iron overload and of multiple chemotherapeutic agents using patient-specific induced pluripotent stem cells (iPSCs) derived models. Her current research employs clinical data, population genomics, and patient-derived iPSCs models to study genetic determinants and mechanisms of drug-induced cardiovascular toxicities. Dr. Rhee's clinic sees cardio-oncology patients and focuses on devising new methods for minimizing cardiovascular complications in that population.
Updates on Cardiovascular Complications of COVID-19

June-Wha Rhee, MD, FACC
Stanford University School of Medicine
Outline

• Brief biology of COVID-19
• Overall epidemiology & spectrum of cardiac complications related to COVID-19
• Cardiac complications
  • Myocardial injury & heart failure
  • Arrhythmia and cardiac arrest
• Available/experimental treatment options
• ACEI/ARB considerations

Since 2020, 15,928 articles have been published on COVID-19!
Basics of SARS-CoV-2

Enveloped + sense ssRNA virus
Genome sequence suggest bat-derived source
96% identical in nucleotide sequence to SARS-CoV, the cause of SARS in 2003

Lung Epithelial Cells (Type II Pneumocyte)
COVID-19 is still on going

• Thus far, there have been in total of 5,460,747 confirmed cases worldwide

• COVID-19 cases have been rapidly rising in the US
  • As of May 25, 2020: there are
    • 1,622,114 total cases (>90K in California)
    • 97,049 deaths (>3700 deaths in California)

At Stanford:
• ~ 90 in patient cases (~20 in ICU).
• 4 deaths.
• 2 cardiac complications (in patients with pre-existing CVD): 1 electrical storm + 1 RV failure
• 1 PE

Case Fatality Rates of COVID-19

- The overall case fatality rate (CFR) of COVID-19 is ~6.3% but varies widely
- More than 80% of infected patients experience mild symptoms and recover without intensive medical intervention → difficult to know the overall prevalence of infection
  - In the case of Diamond Princess: 46.5% asymptomatic at the time of testing

https://coronavirus.jhu.edu/data/mortality
Flu & COVID-19 death rates by age

Elderly patients are particularly vulnerable!

Flu vs COVID-19 death rate, by age

Source: Centers for Disease Control and Prevention (CDC), Chinese Center for Disease Control and Prevention

Onler G et al. JAMA 2020
Causes of COVID-19 associated death

- Cardiac complications are the leading cause of death following respiratory failure

Underlying CVD comorbidities may increase risk for contracting COVID-19 and portend worse outcome.

Case fatality rates for comorbid patients are materially higher than the average population:
- Cancer: 5.6%
- Hypertension: 6.0%
- Chronic respiratory disease: 6.3%
- Diabetes: 7.3%
- **Cardiovascular disease: 10.5%**

High burden of underlying CVD in patients with COVID19 (China)

Chen N. et al.
High burden of underlying CVD among critically ill patients and non-survivors

High burden of underlying CVD among critical ill COVID-19 patients (China)


High burden of underlying CVD among non-survivors (China)

*Lancet 2020, Zhou et al*
Data from the Surgical Outcomes Collaborative (Surgisphere), an international registry, including data from 169 hospitals located in 11 countries in Asia, Europe, and North America.

Total 8910 patients with Covid-19
- 8395 survived to discharge
- 515 died in the hospital

Interestingly, HTN not different between survivors and nonsurvivors
Acute cardiac complications of COVID-19

Existing data suggest COVID-19 leads to

- **Myocardial injury +/- cardiac dysfunction**
  - Direct myocardial insult from the virus
  - Myocarditis
  - Myocardial infarction vs microvascular events
  - Stress CM, demand ischemia
  - Cytokine storm + hemodynamic consequence
  - Hypoxia-induced injury
- **Pulmonary hypertension and RV dysfunction**
- **Arrhythmia, cardiac arrest**

Slide modified from Stanford Cardiology Grand Rounds
Cardiac injury portends worse outcomes

- Myocardial injury, defined as cTn conc. >99th percentile upper-reference limit, is common and prognostic in COVID-19
Pre-existing CVD + cardiac injury = BAD
Case: 37 yo M with CP & Dyspnea x 3 days

- Admitted with 3 days chest pain, dyspnea, and diarrhea
- Hypotensive with BP 80/50 mmHg
Case #1: 37 yo M with CP & Dyspnea x 3 days

- Sputum positive for SARS-CoV-2 (negative for extensive viral panel)
- Marked cardiac biomarker elevation
  - Troponin T > 10,000 ng/L
  - CKMB elevated at 112.9 ng/L
  - NT-proBNP 21,025 ng/L
- No significant coronary artery disease per CT coronary angiogram
- Echo showing markedly decreased cardiac function (LVEF 27%)

→ Diagnosed with presumed myocarditis with cardiogenic shock in the setting of COVID-19. Treated with supportive care + immune modulators with subsequent improvement.

Mechanisms of Cardiac Injury

Overall, irrespective of the underlying mechanism, the presence of cardiac injury portends significantly worse outcome.

Figure modified from Cheng P et al. Curr Cardiol Rep. 2020 Apr 29;22(5):34.
Is there Increased Risk of Arrhythmia with SARS-CoV-2 Infections?
ACC Updates Suggest Possible Increased Arrhythmia in COVID-19 patients

Acute Cardiac Complications of COVID-19

- In a recent case report on 138 hospitalized COVID-19 patients, 16.7% of patients developed arrhythmia and 7.2% experienced acute cardiac injury, in addition to other COVID-19 related complications.

Table 4. Complications and Treatments of Patients Infected With 2019-nCoV

<table>
<thead>
<tr>
<th>Complications</th>
<th>Total (N = 138)</th>
<th>ICU (n = 36)</th>
<th>Non-ICU (n = 102)</th>
<th>P Value³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>12 (8.7)</td>
<td>11 (30.6)</td>
<td>1 (1.0)</td>
<td>.&lt;001</td>
</tr>
<tr>
<td>Acute cardiac injury</td>
<td>10 (7.2)</td>
<td>8 (22.2)</td>
<td>2 (2.0)</td>
<td>.&lt;001</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>23 (16.7)</td>
<td>16 (44.4)</td>
<td>7 (6.9)</td>
<td>.&lt;001</td>
</tr>
<tr>
<td>ARDS</td>
<td>27 (19.6)</td>
<td>22 (61.1)</td>
<td>5 (4.9)</td>
<td>.&lt;001</td>
</tr>
<tr>
<td>AKI</td>
<td>5 (3.6)</td>
<td>3 (8.3)</td>
<td>2 (2.0)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Major Caveat: Exact arrhythmia not defined in the JAMA study.

JAMA 2020, Wang et al

Slide modified from Stanford Cardiology Grand Rounds (Paul Cheng)
Lack of Reports on Arrhythmia

• **Clinical Characteristics of Covid-19 in New York City** (Goyal et al, NEJM 2020)
  - first 393 consecutive patients with Covid-19 in 2 hospitals in New York City: **atrial arrhythmias (17.7% vs. 1.9%, intubated vs no intubated)**

• **Clinical Characteristics of Coronavirus Disease 2019 in China** (Guen et al, NEJM 2020)
  - 51 centers, 1099 patients, **no reported incidence of arrhythmia**

• **Epidemiological and clinical features of 2019-nCoV acute respiratory disease cases in Chongqing municipality, China: a retrospective, descriptive, multiple-center study.** (Qi et al, Medrixv)
  - 267 pt, 3/50 severe pt had trop >0.03, **no arrhythmia reported**

• **Clinical features and outcomes of 2019 novel coronavirus-infected patients with cardiac injury (41 pts)** (Liu et al, medrxiv) (Guangzhou)
  - 5 % with trop > 0.03 (15/291), **no arrhythmia reported**
Summary of COVID-19 cardiac complications

- Patients with underlying CVD have overall poor prognosis
- Patients who suffer from myocardial injury have overall worse outcome
- Potential cardiovascular complications include:
  - myocardial injury and cardiac dysfunction
  - possible arrhythmia, cardiac arrest

Accumulating data suggest that any degree of myocardial injury marked by elevated troponin level, irrespective of the underlying mechanisms, portends significantly worse outcome
Are there any treatments?

Hypothesis of Viral Pathogenesis & Immune Response

Siddiqi, Journal of Heart & Lung Transplantation, 2020
Remdesivir (Gilead)

Remdesivir for the Treatment of Covid-19 — Preliminary Report

• Designed to inhibit Ebola RNA-dependent RNA polymerase (RdRp).

• Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo)
  • Median recovery time: 11 days vs 15 days (RR 1.32, P<0.001).
  • Mortality: 7.1% vs 11.9% (HR 0.7, CI: 0.47 to 1.04)

No. at Risk
Remdesivir 538 481 363 274 183 142 121 98 78 65 3 0
Placebo 521 481 392 307 224 180 149 115 91 78 2 0
Lopinavir-Ritonavir (anti-HIV)?

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

Chloroquine (anti-malaria)?

- Generally used for treatment of malaria and amebiasis.
- Thought to work via multiple mechanisms but the exact mechanism remains unknown.
- Potential cardiotoxicities:
  - QT prolongation ("Quinidine effects") + cardiac arrest: increasing risk of torsades de pointes
  - Cardiac dysfunction (has negative inotropic effects)
  - Possible conduction abnormalities when overdosed

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Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Intubation or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude analysis — hazard ratio (95% CI)</td>
<td>2.37 (1.84–3.02)</td>
</tr>
<tr>
<td>Multivariable analysis — hazard ratio (95% CI)*</td>
<td>1.00 (0.76–1.32)</td>
</tr>
<tr>
<td>Propensity-score analyses — hazard ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>With inverse probability weighting†</td>
<td>1.04 (0.82–1.32)</td>
</tr>
<tr>
<td>With matching‡</td>
<td>0.98 (0.73–1.31)</td>
</tr>
<tr>
<td>Adjusted for propensity score‡</td>
<td>0.97 (0.74–1.28)</td>
</tr>
</tbody>
</table>

No. of events/no. of patients at risk (%)

- Hydroxychloroquine: 262/811 (32.3)
- No hydroxychloroquine: 84/565 (14.9)

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Slide modified from Stanford Cardiology Grand Rounds
Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Multinational registry analysis of the use of hydroxychloroquine or chloroquine

- Total: 96,032 patients with COVID-19
- Hydroxychloroquine: 14,888 patients
Treatments with hydroxychloroquine led to significantly increased risk of ventricular arrhythmia!

Due to safety concern, WHO subsequently advised to temporarily pause ongoing hydroxychloroquine trial (Solidarity)
How about immunomodulators?

COVID-19: consider cytokine storm syndromes and immunosuppression

Puja Mehta • Daniel F McAuley • Michael Brown • Emilie Sanchez • Rachel S Tattersall • Jessica J Manson • et al.

Published: March 16, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)30628-0
COVID-19 and cytokine storm

Premise:
- Prominent lymphopenia, with normal WBC count
- Degree of lymphopenia correlating with severity
- Acute multi-organ failure with high fevers mimic those seen in drug-induced cytokine storm

Hypothesis:
- “Cytokine storm” induced by the virus contribute to the impaired immune response, and hyper-inflammation is part of pathogenesis
IL-6 Level Correlate with Disease Severity Better than other Inflammatory Markers

- Anecdotal effective treatment with Tocilizumab from Italy and China
- Current ongoing trial for IL-6 blockade in COVID19 pts
  - NCT04315298 (New York, Sarilumab)
  - ChiCTR2000029765 (Hubei, China, Tocilizumab)
Tocilizumab Treatment With Some Promise

Effective treatment of severe COVID-19 patients with tocilizumab

Xiaoling Xu, Mingfeng Han, Tiantian Li, Wei Sun, Dongsheng Wang, Bingqin Fu, Yonggang Zhou, Xiaohu Zheng, Yun Yang, Xiuyong Li, Xiaohua Zhang, Aijun Pan, and Haiming Wei

PNAS May 19, 2020 117 (20) 10970-10975;

- 21 consecutive "severe" patient
- 19 discharged from hospital with "rapid improvement."
Additional Immunomodulators

**Glucocorticoids**
- Suppress inflammatory cytokines
- Delayed viral clearance; WHO recommends advises against for Sars-CoV-2 ARDS unless another indication
- Phase 2 RCT: Solumedrol 40 mg q12h for 5 days in ICU level pts w/ PaO2/FiO2 < 200 mmHg (NCT04244591)

**IVIG**
- Complement activation; saturation of Fc receptors on macrophages; and suppression of cytokines/chemokines
- Good safety profile, benefit in MERs & SARS
- Phase 2 RCT: IVIG 0.5g/kg/d for 5 days in pts w/ PaO2/FiO2 < 200 mmHg and/or multi-organ failure (NCT04261426)

**Convalescent Plasma**
- Plasma of recovered donors (protective antibodies)
- Donors: recovered patients > 14 days; females HLA Ab neg; male donors
- FDA expanded access for respiratory failure or shock

Slide from Stanford Cardiology Grand Rounds (Han Zhu)
Summary of COVID-19 treatments

- **Stage I** (Early Infection)
  - Viral response phase
- **Stage II** (Pulmonary Phase)
  - IIA
  - IIB
- **Stage III** (Hyperinflammation Phase)
  - Host inflammatory response phase

**Potential Therapies**

- Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
- Reduce immunosuppression
- Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors

*Slide from Stanford Cardiology Grand Rounds*
ACE2 and COVID-19

SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells

Concerns regarding ACEI/ARB

• Are patients taking ACEI/ARB more likely to get infected with SARS-CoV-2?
• Are COVID-19 patients taking ACEI/ARB worse off?
Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19

Use of ARBs or ACEI did not show any association with Covid-19 among case patients for both ARB and ACEI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio for Covid-19 (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Drugs‡</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive drugs overall</td>
<td>1.53 (1.43–1.63)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>1.16 (1.08–1.24)</td>
</tr>
<tr>
<td>ARBs</td>
<td>1.20 (1.12–1.29)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>1.28 (1.18–1.38)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1.42 (1.33–1.51)</td>
</tr>
</tbody>
</table>

*Use of ARBs or ACEI did not show any association with Covid-19 among case patients for both ARB and ACEI.

†Odds ratios were adjusted for age, sex, and comorbidities.

‡Antihypertensive drugs overall comprised ACE inhibitors, ARBs, and calcium-channel blockers.

A population-based case–control study in the Lombardy region of Italy.
A total of 6272 case patients with COVID-19 were matched to 30,759 beneficiaries.
• Retrospective cohort study conducted at the Cleveland Clinic Health System in Ohio and Florida
• 18,472 patients tested for COVID-19, 1,735 patients were tested pos.
• No association between ACEI or ARB use and COVID-19 test positivity
Data from the Surgical Outcomes Collaborative (Surgisphere), an international registry, including data from 169 hospitals located in 11 countries in Asia, Europe, and North America.

Total 8910 patients with Covid-19 (515 death)

No increased risk of in-hospital death was found to be associated with the use of ACE inhibitors (2.1% vs. 6.1%; OR, 0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (6.8% vs. 5.7%; OR, 1.23; 95% CI, 0.87 to 1.74).
• Retrospective analysis of multicenter data from China including 1128 adult patients with hypertension diagnosed with COVID-19

• The incidence of the 28-day all-cause death among patients who had inpatient treatment with ACEI/ARB is significant lower compared with ACEI/ARB non-users.
Current recommendations regarding ACE/ARB Use During COVID-19 Out Break

AHA/ACC/HFSA Joint Statement

“We understand the concern – as it has become clear that people with cardiovascular disease are at much higher risk of serious complications including death from COVID-19. However, we have reviewed the latest research – the evidence does not confirm the need to discontinue ACE-i or ARBs, and we strongly recommend all physicians to consider the individual needs of each patient before making any changes to ACE-i or ARB treatment regimens,” said Robert A. Harrington, M.D., FAHA, president of the American Heart Association, Arthur L. Bloomfield Professor of Medicine and chair of the department of medicine at Stanford University.

Don’t change and continue taking them!!
Incidence of hospitalization for acute MI is dropping...

Data from Kaiser Northern CA (43,017,810 person-weeks from January 1 through April 14, 2020) note that significant drop in acute MI during the COVID-19 period

- The weekly rates of hospitalization for acute MI decreased by up to 48%.

NEJM May 19, 2020 DOI: 10.1056/NEJMc2015630

Need to remind patients to seek medical attention for acute heart care!
In Summary...

1. Patients with underlying CVD have overall poor prognosis

2. Patients who suffer from myocardial injury have overall worse outcome, irrespective of the underlying mechanisms.

3. Many treatments are on the horizon, but effectiveness may depend on overall disease stage of COVID-19.

4. Currently, there is no data to support increased infectivity or worse outcome with the use of ACEI/ARB. Therefore, please continue!

5. It is important to remind patients to seek medical attentions for any symptoms or signs concerning for acute MI
Thank you for your attention!