COVID-19 and the Heart

COVID-19, ACE2, and the Cardiovascular Consequences[1,2]

- Viral infections are dependent on cellular entry of the virus that afterward uses the cellular machinery of the host to replicate multiple viral copies, which are subsequently shed by the host cell.
- Coronaviruses such as SARS-CoV-2 and SARS-CoV-1 are known to use the host protein angiotensin-converting enzyme-2 as a co-receptor to gain intracellular entry into the lungs, heart and brain.
- ACE2 is a membrane-bound peptidase with the majority of the protein that comprises the NH2-terminal peptide domain, including the catalytic site oriented extracellularly.
- ACE2 is expressed in essentially all tissues, with greatest activity in the ileum and kidney, followed by adipose tissue, heart, brain stem, lung, vasculature, stomach, liver, and nasal and oral mucosa based on activity data in the mouse that generally parallel ACE2 mRNA levels in humans.
- As to the mechanism for the intracellular entry by SARS- CoV-2 and SARS-CoV, the viral coat expresses a protein termed SPIKE (S protein) that contains a receptor-binding region that binds to the extracellular domain of ACE2 with high affinity.
- ACE2 internalization by SARS-CoV-2 would potentially result in down-regulation of ACE2 expression and consequent unabated angiotensin II activity ➡ LV hypertrophy and fibrosis, impaired LV function, arrhythmias.
- Reduced expression of ACE2 in the vasculature may promote endothelial dysfunction and inflammation and exacerbate existing atherosclerosis, hypertension and diabetes.

Heart[3,4]

Cardiac involvement is a prominent feature in COVID-19 and is associated with a worse prognosis.

Mechanisms

Direct myocardial injury by virus SARS-CoV-2 enters human cells by binding to angiotensin-converting enzyme 2 (ACE2) receptor, a membrane bound which is highly expressed both in heart and lungs. The binding of SARS-CoV-2 to ACE2 can result in alteration of ACE2 signaling pathways ➡ acute myocardial injury.

Altered myocardial oxygen demand-supply relationship due to systemic infection, respiratory failure and hypoxia ➡ acute myocardial injury.

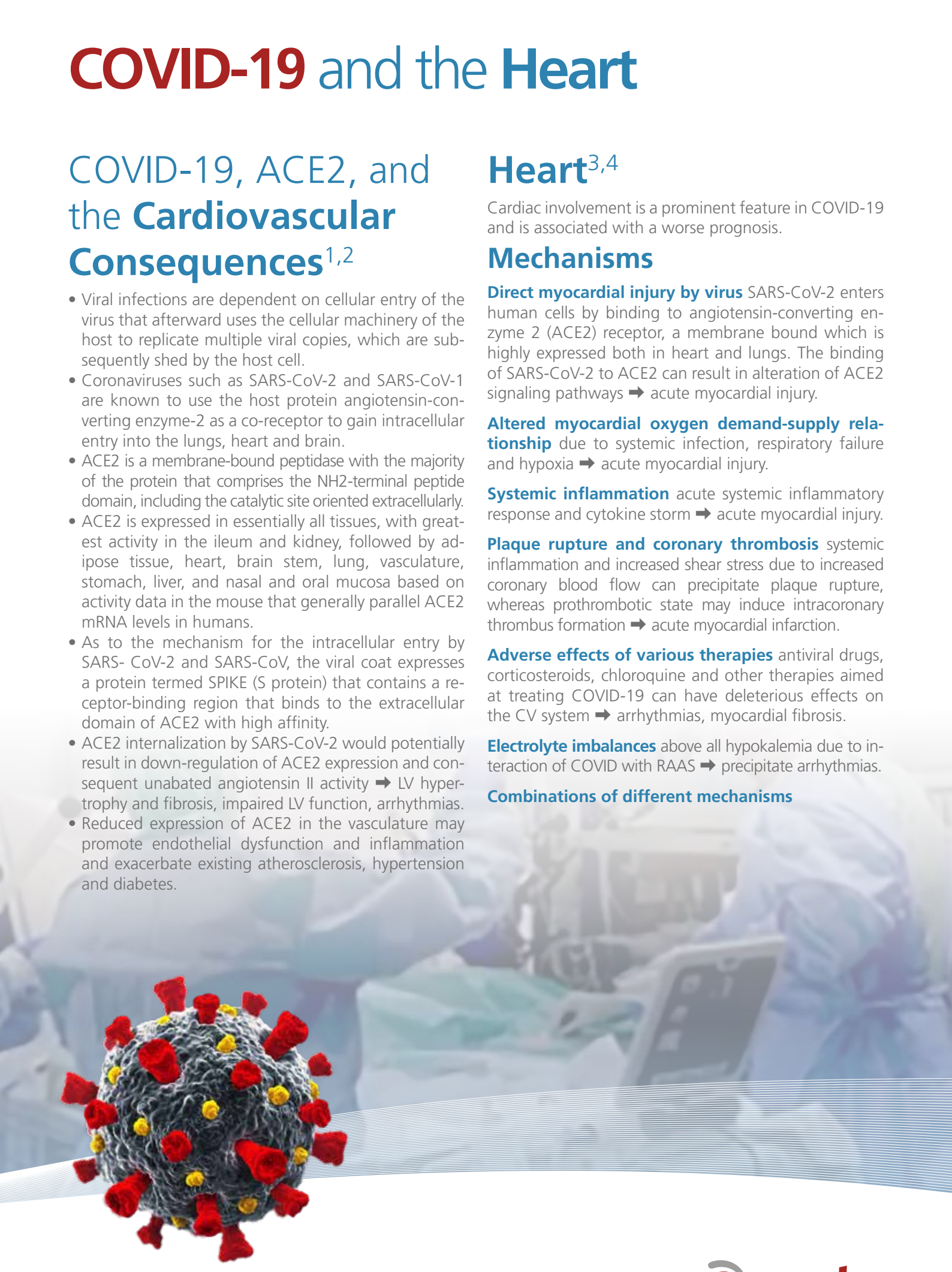
Systemic inflammation acute systemic inflammatory response and cytokine storm ➡ acute myocardial injury.

Plaque rupture and coronary thrombosis systemic inflammation and increased shear stress due to increased coronary blood flow can precipitate plaque rupture, whereas prothrombotic state may induce intracoronary thrombus formation ➡ acute myocardial infarction.

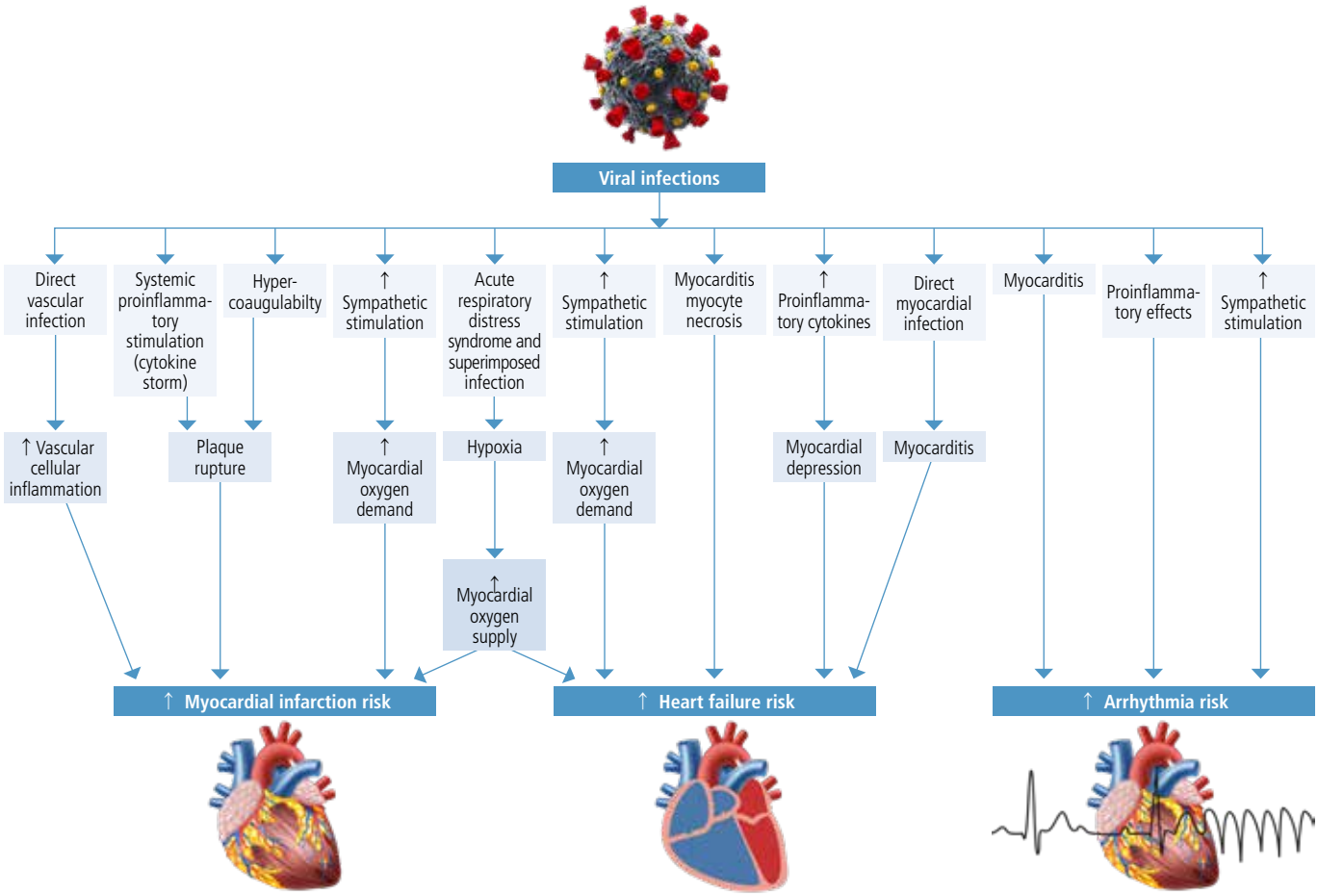
Adverse effects of various therapies antiviral drugs, corticosteroids, chloroquine and other therapies aimed at treating COVID-19 can have deleterious effects on the CV system ➡ arrhythmias, myocardial fibrosis.

Electrolyte imbalances above all hypokalemia due to interaction of COVID with RAAS ➡ precipitate arrhythmias.

Combinations of different mechanisms



Potential Mechanisms for Acute Effect of Viral Infection on CV System[5]



COVID-19 and the **Cardiovascular Consequences**[4,6]

The overall incidence of acute cardiac injury varies between 8% and 12% of the positive cases.

Acute cardiac injury has been consistently shown to be a strong negative prognostic marker in patients with COVID-19. The severity of COVID-19 is associated with acute cardiac injury, and acute cardiac injury is associated with death.

Both tachy– and brady-arrhythmias are known to occur in COVID-19. A study describing clinical profile and outcomes in 138 Chinese patients with COVID-19 reported 16.7% incidence of arrhythmia. The incidence was much higher (44.4%) in those requiring ICU admission as compared to those not requiring ICU admission (8.9%).

CV co-morbidities increase the mortality rate. Chinese Center for Disease Control and Prevention described clinical outcomes in 44672 confirmed cases of COVID-19; overall mortality rate = 2.3%; in patients with hypertension = 6%; patients with CVD = 10%.

These data highlight the need to effectively monitor heart health in order to limit cardiac complications in patients infected with COVID-19.

Cardiac Complications in COVID-19 patients
Chinese experience[7-11]

Author/Journal	Study Population	Cardiac Manifestation	Mortality
Huang C/Lancet	41	Shock (7%)	15%
Wang D/JAMA	118	Shock (8.7%) Arrhythmia (16.7%) Myocardial injury (7.2%)	4.3%
Shi S/JAMA	416	Chest pain (3.4%) S-T depression (0.7%)	13.7%
Zhou F/Lancet	191	Heart failure (23%) Hypotension (1%) HR>125 bpm (1%)	28.2%

The **echocardiographic features** in COVID-19 patients[12]

	Echocardiographic Findings	Cardiac Manifestation	Pathophysiology
Hyperdynamic cardiac function	Increase LV cardiac output and ejection fraction with/without decrease of peripheral vascular resistance	Shock (7%)	Cardiac stress response to systemic inflammation, increase of LV preload by fluid resuscitation, decrease of LV afterload by reduced peripheral vascular resistance
Acute stress-induced (takotsubo) cardiomyopathy	LV segmental contraction abnormalities and apical ballooning	Shock (8.7%) Arrhythmia (16.7%) Myocardial injury (7.2%)	Elevated levels of circulating plasma catecholamines and its metabolites, microvascular dysfunction, inflammation, estrogen deficiency, spasm of the epicardial coronary arteries
Right ventricular enlargement Acute pulmonary hypertension and right ventricular enlargement	Ratio right/left ventricular area > 0.6; IVS protruded to the left ventricle; decreased systolic and/or diastolic function of RV; changes in frequency and rhythm of pulmonary blood flow, tricuspid regurgitation	Chest pain (3.4%) S-T depression (0.7%)	Increased pulmonary vascular resistance, embolism, pulmonary vasospasm, hypercapnia and inflammation; fluid overload; unsuitable mechanical parameter settings
Diffuse myocardial inhibition	Decreased systolic and/or diastolic function of the whole heart	Heart failure (23%) Hypotension (1%) HR > 125 bpm (1%)	Severe hypoxia and inflammation; the circulatory failure is often caused by diffuse cardio-depression and the decrease of vascular tension caused by lactic acidosis

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Role of Echocardiography
in Patients with Suspected or Proven COVID-19[13]

Recommendation of UK Intensive Care Society
Indications - management

Cardiac ultrasound

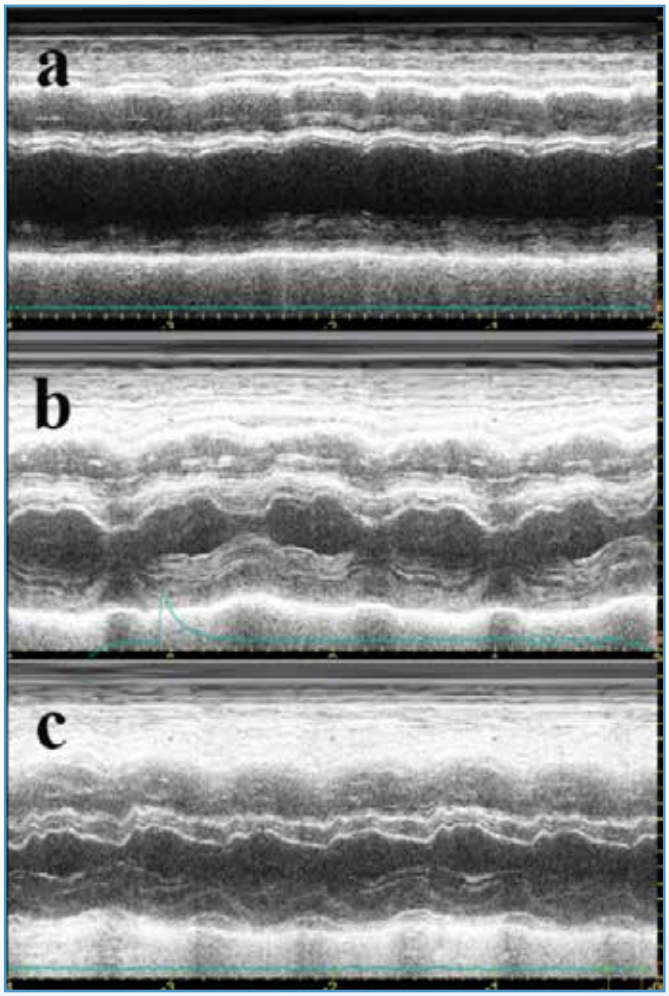
Monitoring of left heart function in patients with acute cardiomyopathy, presumably secondary to viral myocarditis.

Monitoring of right heart function in patients who are at risk of suffering acute cor pulmonale secondary to

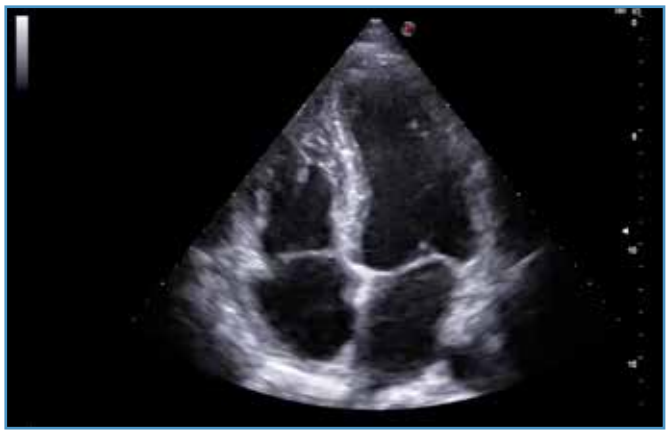
- hypoxic vasoconstriction
- ventilator induced lung injury
- pulmonary embolism ➡ patients with COVID are at a higher risk of disseminated intravascular coagulation[14]
- thrombotic complications in ICU patients with COVID is 31%

Echocardiographic Features of COVID-19-induced **Fulminant Myocarditis** in China[15]

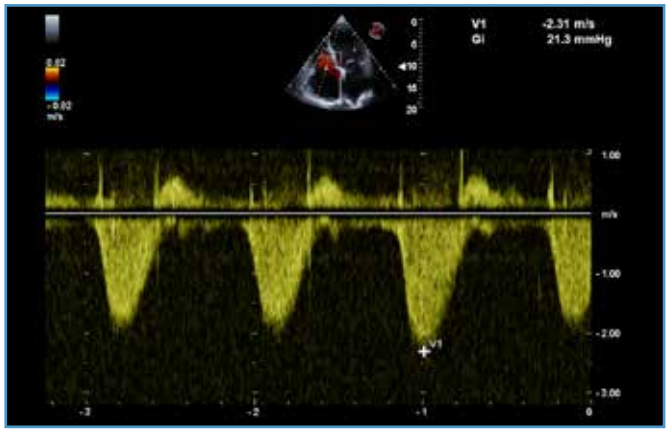
A 63-year-old male was admitted to the hospital due to coughing of white sticky sputum and fever up to 39.3°, accompanied by shortness of breath and chest tightness after activity. He had no history of heart disease or hypertension.



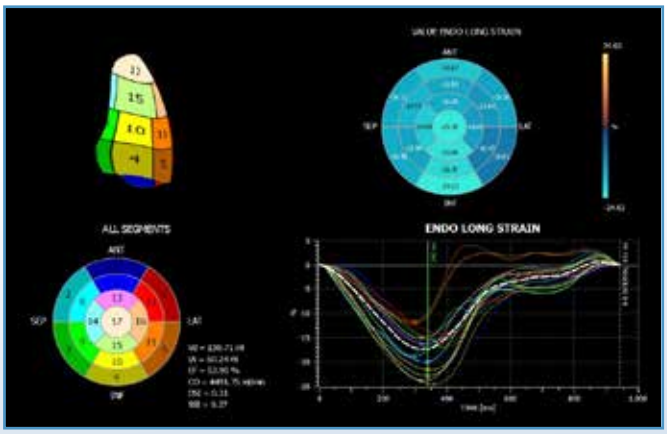
The echocardiographic left ventricular M-mode images of the 1st day (a), the 10th day (b) and the 17th day after admission (c).
(a) left ventricular diameter was enlarged and ejection fraction was decreased
(b) edema of left ventricular wall and improvement of ejection fraction;
(c) normal left ventricular ejection fraction and wall thickness



Apical 4-chamber view to assess the right/left ventricle ratio



Measurement of tricuspid regurgitation velocity to estimate pulmonary artery pressure



Strain echocardiography to detect left ventricular segmental contraction abnormalities

American Society of Echocardiography Guidelines

Cardiovascular disease is the comorbidity that carries with it the highest death rate in COVID-19 patients, at about 10.5 percent.

For this reason, risk of cardiovascular complications in the setting of COVID-19, including pre-existing cardiac disease, acute cardiac injury and drug-related myocardial damage, will require the use of echocardiography in the care of some patients with suspected or confirmed COVID-19.

The provision of echocardiographic services remains crucial during the novel coronavirus (COVID-19, SARS-CoV-2) outbreak.

To minimize risks to cardiac ultrasound staff, the American Society of Echocardiography (ASE) commissioned a group of experts to issue a statement outlining recommendations to improve safety and reduce the potential for COVID-19 cross contamination.

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EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel

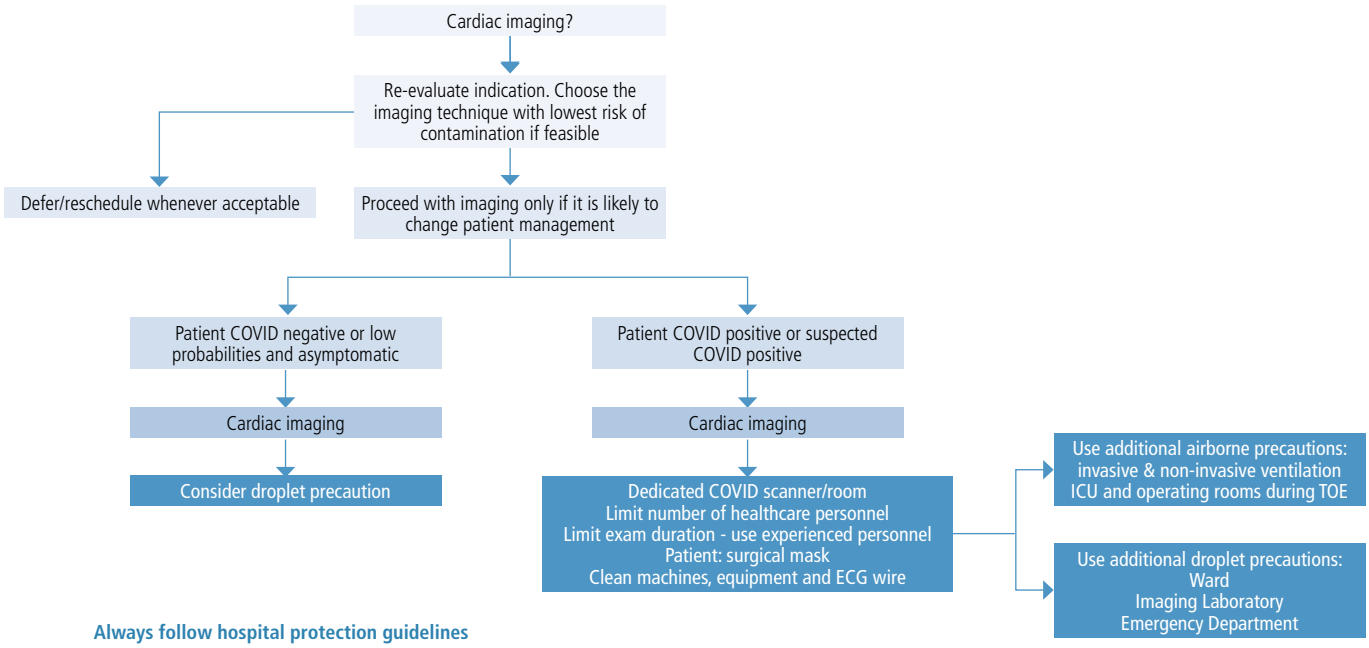
Indications

- A focused cardiac ultrasound study (FoCUS) is recommended to reduce the duration of exposure
- The need for echocardiography might expand further as we understand more about COVID-19, with early reports indicating that patients with established cardiovascular disease and cardiovascular risk factors have worse prognosis than others, and are more likely to be admitted to hospital and need respiratory support
- Echocardiography should be restricted to patients with cardiovascular instability or signs of right ventricular dysfunction or pulmonary hypertension.
- Lung ultrasound to detect COVID-19 pneumonia is also useful. Thickening of the pleurae, the appearance of B-lines, and lung consolidation indicate pneumonia, with pleural effusions rarely reported. Due to its bedside availability, scanning of the lungs by ultrasound can be performed as a quick diagnostic tool.

Procedure & Cleaning

- The echocardiographic study will usually be performed in the ICU or in emergency rooms in critically ill patients. Less critical patients are usually examined in their ward rooms. Dedicated room(s) may be prepared in the echocardiographic lab, where unnecessary equipment can be removed to facilitate cleaning of the room.
- Protecting the echocardiographic machines with custom-made covers may be possible if available, but, if not, other protective equipment can be fashioned using local businesses and some ingenuity. It is, however, important not to cover the screen in a way that reduces the view for the echocardiographer.
- To facilitate cleaning of the scanner, all additional 3-D and single-Doppler probes should be removed before scanning starts, if they are not needed for proper diagnosis. ECG leads should also be removed.
- Moderately warm water and a mild detergent are the basis for equipment cleaning in all cardiac imaging machines, including the echocardiographic probe. An ordinary water-soluble disinfectant should also be added, but not on the membrane. A non-alcoholic disinfectant should be used on the echocardiographic probe
- Patients placed in the left lateral position with the scanner positioned on the right side of the bench will result in the longest possible distance. A surgical mask on the patient will also reduce contamination by air droplets

Suggested **considerations** and **precautions** before and during cardiac imaging as recommended by EACVI



Always follow hospital protection guidelines

ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic

- Autopsies of patients with COVID-19 infection revealed infiltration of the myocardium by interstitial mononuclear inflammatory cells.
- COVID-19 infections are associated with increased cardiac biomarker levels due to myocardial injury that are associated with infection-induced myocarditis and ischaemia.
- Myocarditis appears in COVID-19 patients several days after initiation of fever.
- Mechanisms of SARS-CoV-2-induced myocardial injury may be related to upregulation of ACE2 in the heart and coronary vessels.
- Echocardiography can be performed bedside to screen for CV complications and guide treatment. POCUS, FoCUS and critical care echocardiography are probably the preferred modalities to image patients with COVID-19.
- In COVID-19 infected patients, echocardiography should focus solely on the acquisition of images needed to answer the clinical question in order to reduce patient contact with the machine and health-care personnel.

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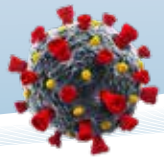

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