Review Article

Beyond the Ventilator - Cardiovascular Management in SARS-CoV-2 Infection

Amy L. Kloosterboer, Melissa A. Vogelsong, Jessica L. Brodt

Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University, Stanford CA, United States

Abstract

The novel corona virus, severe acute respiratory syndrome coronavirus 2 has spread worldwide since late 2019, with clinical manifestations of coronavirus disease 2019 (COVID-19) ranging from asymptomatic to respiratory impairment to multiorgan dysfunction with life-threatening cardiovascular complications. The mechanism of cardiovascular involvement is likely multifactorial, hypothesized to include direct myocardial injury, secondary injury due to the inflammatory response, and macro- and microthrombotic complications due to hypercoagulability. Acute cor pulmonale and pulmonary embolism are cardiovascular causes of serious morbidity and mortality, and myocarditis and Takotsubo syndrome have also been reported. It is not clear if arrhythmias represent a primary viral effect or a secondary effect of disease severity, though certain pharmacotherapies such as hydroxychloroquine may increase this risk. Point-of-care ultrasound and echocardiography are important tools for the screening and monitoring of these potential complications. Cardiovascular decompensation must be managed supportively with the escalation of vasoactive support, inhaled vasodilators, and consideration of mechanical circulatory support. Many questions remain and ongoing study is required to optimize care of the patient with cardiovascular complications of COVID-19.

Keywords: Cardiovascular, cor pulmonale, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2

Introduction

Since its appearance in late 2019, the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for over 29 million cases of coronavirus disease 2019 (COVID-19) worldwide and over 930,000 deaths as of September 16, 2020.[1] While a major emphasis of treatment for these patients focuses on ventilatory strategies and challenges, SARS-CoV-2 may have significant effects on the cardiovascular system impacting gas exchange, morbidity, mortality, and therapeutic goals. Epidemiological studies in China, Italy, and Sweden have demonstrated increased risk of fatality for patients with COVID-19 with underlying cardiovascular disease, hypertension, and diabetes.[2-4] In addition, patients with myocardial injury, usually diagnosed by elevated cardiac biomarkers, have higher rates of severe disease, admission to the intensive care unit (ICU), and mortality.[5] This review will discuss known and predicted effects of SARS-CoV-2 on the cardiovascular system including pathophysiology, clinical syndromes, diagnosis, and management.

Access this article online

Quick Response Code:

Website: www.ijrc.in

DOI: 10.4103/ijrc.ijrc_105_20

Biochemical Pathophysiology

The underlying pathophysiology of myocardial damage in COVID-19 remains unclear and is likely multifactorial. SARS-CoV-2 enters cells via a transmembrane spike protein that binds angiotensin-converting enzyme 2 (ACE-2).[6] This ACE-2 receptor is present on type II pneumocytes and the virus' entry into these cells is theorized to contribute to lung injury.[7] This receptor has also been documented on cardiac pericytes and viral RNA has been identified in cardiac myocytes on autopsy, leading to biologic plausibility for direct cardiac injury.[8,9] Damage may also occur via the inflammatory response. COVID-19 is associated with elevated inflammatory markers such as C-reactive protein and interleukin-6 which may contribute to cytokine-mediated

Address for correspondence: Dr. Jessica L. Brodt, Stanford University, Department of Anesthesiology, Perioperative and Pain Medicine, 300 Pasteur Dr, Stanford 94305, CA, United States. E-mail: jbrodt@stanford.edu

How to cite this article: Kloosterboer AL, Vogelsong MA, Brodt JL. Beyond the ventilator - Cardiovascular management in SARS-CoV-2 infection. Indian J Respir Care 2021;10:S43-9.

Received: 22-09-2020 **Revised:** 20-01-2021
Accepted: 14-02-2021 **Published:** 29-04-2021

cardio depressant effects.[10,11] Elevations in inflammatory biomarkers in non-COVID-19 patients have been associated with an increased risk of cardiovascular damage independent of cardiac risk factors.[12] Such inflammation may also contribute to hypercoagulability with additional myocardial injury via microthrombi.[9,13]

Clinical Syndromes

Right ventricular failure and cor pulmonale

Any serious lung infection with significant interstitial or airway inflammation may increase pulmonary vascular resistance (PVR), leading to right ventricular (RV) dysfunction and cor pulmonale.[13,14] COVID-19 is no exception. The RV generally works against low vascular resistance and thus is very sensitive to changes in afterload. Increased PVR causes increased RV strain and increasing RV work, resulting in increased myocardial oxygen demand, decreased coronary perfusion, and decreased oxygen delivery. This leads to worsening ischemia and RV dysfunction.[15]

There are multiple complications of SARS-CoV-2 infection, which may contribute to RV failure, including hypoxia and hypercarbia-mediated increases in PVR due to acute respiratory distress syndrome (ARDS), elevated intrathoracic pressures from low pulmonary compliance and mechanical ventilation, pulmonary emboli (PE), and myocardial ischemia.[16]

In non-COVID-19 ARDS, the incidence of RV dysfunction ranges from 22% to 50% and is associated with increased mortality.[17] This finding has also been seen in COVID-19 related ARDS, with the presence of RV longitudinal strain impairment predicting increased risk of mortality.[18] ARDS is characterized by a heterogeneous pattern of lung parenchymal injury with areas of lung over-distension and atelectasis with poor pulmonary compliance, both of which can lead to elevations in PVR.[19,20] Moreover, hypoxemia augments hypoxic pulmonary vasoconstriction, further increasing RV afterload and propagating the RV dysfunction spiral.

The effects of a lung-protective ventilation strategy on RV function can be difficult to predict. The increased peak end-expiratory pressures (PEEP) used have the potential to decrease RV preload and increase RV afterload, decreasing RV cardiac index.[21,22] However, improved alveolar recruitment and oxygenation with the subsequent reduction in hypoxic pulmonary vasoconstriction may relieve RV afterload and enhance RV function.[23] Poor lung compliance from ARDS in addition to high levels of PEEP also contributes to elevations in plateau pressure. Elevated plateau pressures correlate with cor pulmonale and mortality, with a marked increase in mortality seen in patients with evidence of right heart dysfunction when plateau pressure rises above 26 cm H_2O.[24] Driving pressure (the difference between plateau pressure and PEEP) >18 cm H_2O, $PaCO_2$ >48 mmHg, and PaO_2/FiO_2 ratio <150 are also associated with increased risk of acute cor pulmonale in ARDS.[25]

Pulmonary thromboembolism

Patients with COVID-19 are at a higher risk of developing venous thromboembolism (VTE) and subsequent pulmonary embolism likely related to inflammation and cytokine release in the setting of immobility. It has also been proposed that SARS-CoV-2 can lead to vasculitis/endothelitis which may further increase the risk of microangiopathy and capillary thrombi.[26,27] Investigators in three Dutch critical care units found up to 27% of COVID-19 patients experienced symptomatic VTE/PE.[28] Increased PVR due to mechanical obstruction and localized hypoxic pulmonary vasoconstriction can cause significant RV dysfunction, especially in the setting of other risk factors for elevated PVR. Among hemodynamically stable non-COVID-19 patients, any PE-related cardiac dysfunction increases mortality.[29] This etiology is a leading hypothesis in cases of unexpected deaths in COVID-19 patients, with many case reports of acute cor pulmonale.[30]

COVID-19-associated PE is not limited to the inpatient setting, as demonstrated by an approximately three-fold higher incidence of DVT and proximal PE found in unexplained out-of-hospital deaths in Paris during a COVID-19 outbreak compared to the previous year.[31] Patients may develop VTE/PE at any time point during their course of COVID-19, including those with only mild respiratory illness or following discharge from the hospital, necessitating continued clinician awareness in the outpatient setting.[32]

Myocarditis

Multiple case reports have documented myocarditis among patients with COVID-19, diagnosed by multimodality imaging and endomyocardial biopsy.[33-35] Overall prevalence remains unknown given the variability in resource availability and diagnostic testing utilization. A systematic review identified 9 case reports of myocarditis and two poor-quality retrospective studies reported at least 14 patients with possible myocarditis.[36] Common presenting symptoms included dyspnea (82%), coughing (55%), fever (55%), and chest pain (55%), making the differentiation between COVID-19-related lung disease and myocarditis difficult upon initial presentation. Only one of the nine reported cases died, notably from a non-myocarditis-related cause. The retrospective analyses lacked information regarding endomyocardial biopsy or magnetic resonance imaging, making it impossible to conclude if patients truly had myocarditis or had cardiac manifestations of severe systemic illness. The mechanism of myocarditis is not clear – some authors theorize direct viral injury, while others claim the myocarditis is demonstrative of the overall inflammatory state.[37-39] Further research is required to confirm the mechanism of SARS-CoV-2-causing acute myocarditis.

Takotsubo syndrome

A handful of case reports and case series have documented the occurrence of Takutsubo syndrome (TTS) in patients with COVID-19, though the overall incidence is unknown.[40-43] A comprehensive review of these publications identified 16

published cases of TTS identified by echocardiography.[44] Of the 11 cases with available individual patient data, 90.1% demonstrated an elevated troponin T/I level and 90.1% exhibited left ventricular dysfunction while one patient had biventricular wall motion abnormalities. Insufficient data is provided to compare baseline severity of illness of these patients; however, 90.1% demonstrated clinical or echocardiographic improvement. Overall, 12/16 (75%) patients were ultimately discharged, two progressed to veno-venous extracorporeal membrane oxygenation (ECMO) for respiratory failure, and three died. Takotsubo syndrome should be considered in COVID-19 patients who present with evidence of myocardial damage manifested by clinical symptoms, elevated cardiac biomarkers, or electrocardiographic changes. In a cohort study comparing 1914 patients admitted for acute coronary syndrome before versus during the COVID pandemic, a significant increase in TTS was noted, from 1.5% to 1.8% pre-COVID to 7.8% from March 1 to April 30, 2020.[45] Other authors have noted a stable incidence.[46] Although further research is required, TTS should remain on the differential for clinicians in both SARS-CoV2 positive and negative patients.

Arrhythmia

The causal link between COVID-19 and cardiac arrhythmias remains unclear with generally low-level evidence. Initial reports raised concern for increased risk of arrhythmia in COVID-19 infections, with an early report from Wuhan, China documenting an overall arrhythmia rate of 17% in 138 hospitalized patients and 44% among those admitted to the ICU.[47] Other data suggest the prevalence of arrhythmias in clinically stable patients may actually be quite low –9% in a single-day snapshot of 132 non-critically ill inpatients.[48] In a review of 700 hospitalized COVID-19 patients, multivariate analysis revealed independent associations between ICU admission and cardiac arrest, atrial fibrillation, and non-sustained ventricular tachycardia, suggesting a possible association between cardiac arrest and arrhythmias with the severity of disease, rather than a causal effect of the virus itself.[49]

Certain pharmacotherapies that have been used to treat COVID-19 are known to prolong the QT interval and increase the risk of ventricular arrhythmias, including torsades de pointes.[50,51] In a systematic review of 1,515 COVID-19 patients treated with chloroquine or hydroxychloroquine, 10% developed QT prolongation and 2 treated with high dose chloroquine developed ventricular arrhythmia.[50] Notably, current evidence suggests that these therapies are ineffective for the treatment of COVID-19.[52-54] Serious consideration should be given to baseline and regular electrocardiographic monitoring of COVID-19 patients, particularly those treated with these agents or who are critically ill.

Diagnosis

Considering the frequency and variety of cardiac complications associated with COVID-19, point-of-care ultrasound (POCUS) including transthoracic echocardiography (TTE) is an important tool in evaluating and managing patients with COVID-19. In non-COVID-19 patients, bedside echocardiography has demonstrated the high utility and often changes clinical management. As an example, providers using the Focused Intensive Care Echocardiography format found new clinical information in 41/60 (68%) of examinations performed, resulting in a change in clinical management in 28/60 (47%).[55] Literature in COVID-19 patients to date is less robust. A retrospective analysis of 749 patients admitted with COVID-19 reported 9.6% of patients underwent TTE, most commonly for evaluation of hemodynamic instability (29.2%) or concern for a major cardiovascular event (45.8%).[56] However, in those scanned, echocardiographic findings changed clinical management in nearly 40% of patients. Multiple institutions have developed POCUS protocols to ensure providers can efficiently obtain all relevant information and limit additional exposures.[57,58]

The American Society for Echocardiography (ASE) provides a suggested workflow in suspected or confirmed COVID-19 cases, including recommendations to mitigate the risk of transmission to healthcare workers.[59,60] Figure 1 shows the ASE modified POCUS protocol for initial cardiopulmonary assessment in COVID-19 patients. This is an excellent resource for providers, and assuming provider expertise and optimal ultrasound windows, these views can reveal many serious cardiopulmonary pathologies as well as guide estimates of fluid status and indicate possible deep venous thrombosis. The ASE recommendations to mitigate risk to healthcare workers include having an experienced provider perform an initial POCUS examination and proceeding to a complete TTE only if that exam is insufficient in answering the clinical question.

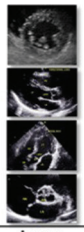
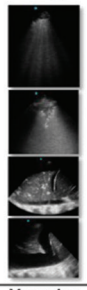
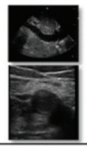
Treatment

Right ventricle protective ventilation

Lung protective ventilation has become the standard of care for ARDS treatment since the publication of the ARDSNet protocol in 2000.[61] However, while these strategies have shown significant oxygenation and mortality benefit, they may carry risk to RV function as described above, and high-quality data on optimal RV protective strategies remains lacking. There is evidence to suggest that prone ventilation may improve RV function, which may contribute to the mortality benefit seen in proning patients with ARDS.[62,63] Regardless of the lung-protective strategy utilized, providers should remain vigilant for any evidence of RV dysfunction.

Inhaled pulmonary vasodilators

Inhaled pulmonary vasodilators such as nitric oxide or prostacyclins may improve oxygenation and relieve RV strain. Owing to their inhalational mode of administration, these vasodilators act directly on the vessels supplying aerated regions of the lung, thus locally decreasing PVR and improving ventilation-perfusion matching. *In vitro*, nitric oxide has been found to inhibit cytotoxic effects of SARS-CoV-2, which along with the theorized improvement in ventilation-perfusion

COVID19 POCUS Protocol	Structure Imaged	Assessment	Disease Associations
Cardiac 	Left Ventricle	Size, Global and Regional Function	Myocarditis ACS Cardiomyopathy Shock
	Right Ventricle	Size and Function; TR for PASP if available	PE Cardiomyopathy
	Pericardium	Effusion	Tamponade
	Valves	Gross Regurgitation or stenosis	Pre-existing CV disease
Lung 	8 or 12 point exam	B Lines (A lines, pleural sliding are normal)	Edema or Pneumonia
		Sub-pleural Consolidation Thickened Pleura	Pneumonia ARDS
		Lobar consolidation with air Bronchograms	Pneumonia ARDS
		Effusion	CHF
Vascular 	JVP or Subcostal IVC	Fluid Status	CHF, hypovolemia
	+/- Leg Veins*	2 point compression*	DVT

*Leg veins may be assessed if the operator has training in this technique, clinical suspicion exists, and the sonographer is not available.
ACS, acute coronary syndrome; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; PE, pulmonary embolism; CV, cardiovascular; ARDS, acute respiratory distress syndrome; JVP, jugular venous pulsation; IVC, inferior vena cava. CHF, congestive heart failure; DVT, deep vein thrombosis.

Figure 1: American Society of Echocardiography point of care ultrasound protocol for coronavirus disease 2019 confirmed or suspected patients. *Leg veins may be assessed if the operator has training i this techniques, clinical suspicion exits and the sonographer is not available. ACS: Acute coronary syndrome, TR: Tricuspid regurgitation, PASP: Pulmonary artery systolic pressure, PE: Pulmonary embolism, CV: Cardiovascular, ARDS: Acute respiratory distress syndrome, JVP: Jugular venous pulsation, IVC: Inferior vena cava, CHF: Congestive heart failure, DVT: Deep vein thrombosis

matching provide physiological basis for treatment in COVID-19 ARDS.[64]

In pre-COVID studies, inhaled pulmonary vasodilators have been shown to improve refractory hypoxemia but not to decrease mortality in ARDS.[65,66] During the 2002 SARS outbreak, inhaled nitric oxide (iNO) was shown to improve arterial oxygenation and allow for non-invasive ventilatory support to be discontinued in spontaneously breathing patients, providing hope that this would prove efficacious in COVID-19 as well.[67] To this point, limited literature has revealed no benefit when iNO has been used non-selectively in COVID-19 patients.[68-70] One very small (n = 4) subset of COVID-19 patients with documented RV dysfunction that received iNO showed a trend toward improved oxygenation.[70] Clearly, additional study is needed with such a small sample size; however, this finding hints at the possible utility of these agents in managing hypoxemia in COVID-19 patients with RV dysfunction. Note that resources will vary between centers and local protocols may exist that limit nebulizer therapy (and therefore use of prostacyclins) in COVID-19 due to possible aerosol generation and viral exposure.

Multiple registered trials are ongoing to assess the efficacy of inhaled pulmonary vasodilators in COVID-19. Until additional data are reported, it is empirically reasonable to trial inhaled pulmonary vasodilators in patients with refractory hypoxemia, particularly in the setting of concurrent RV dysfunction.

Vasopressors and inotropes

Shock is common among critically ill patients with COVID-19. In a review of 1,099 COVID-19 patients in China, 1.1% developed shock, while a more recent meta-analysis showed an incidence of the shock of 4.7% among 47,344 patients with confirmed COVID-19.[71,72] The incidence in critically ill patients is significantly higher, with reports of up to 35%-66%.[73,74] There are no trials evaluating vasoactive choice in COVID-19 related shock. Critical care recommendations include fluid resuscitation and vasopressor choice consistent with prior Surviving Sepsis Guidelines.[75,76] Such guidelines recommend the use of norepinephrine as first-line in COVID-19 patients with shock.[76] The addition of vasopressin, more potent inotropes such as epinephrine, or inodilators such as dobutamine or milrinone may provide additional benefit in cardiogenic or mixed shock. An international survey of 1000 intensivists confirmed that >50% of providers use vasopressors to manage COVID-19 patients requiring treatment in the ICU, and 54% of providers utilized echocardiography to help characterize their shock state, fluid responsiveness, and ultimately guide vasopressor choice.[77]

As there are no trials guiding the choice of vasopressor in COVID-19 patients, it is reasonable to utilize clinical tools including physical exam and echocardiography to evaluate the cause of shock and to then treat based on existing Surviving Sepsis Guidelines and presumed physiology. Treatment should be goal-directed. As institutions and societies continue to amass experience, there may be future evolutions in treatment algorithms for critically ill COVID-19 patients.

Mechanical circulatory support

Mechanical circulatory support represents an umbrella category of devices used to assist the failing cardiovascular system. While there may be some role for devices such as intra-aortic balloon pumps and percutaneous ventricular assist devices for isolated cardiogenic shock, the frequent coexistence of respiratory failure in SARS-CoV-2 infection has shifted the focus to the use of ECMO. Following an increase in use after the 2009 influenza A (H1N1) pandemic, ECMO offers a resource-intensive but potentially life-saving therapy for refractory respiratory or cardiac failure.[78,79] Current evidence for its use during the coronavirus pandemic is limited to case series and registry data, with 2527 runs reported for confirmed COVID-19 in the ELSO Registry as of September 15, 2020.[80] The vast majority of these cases have been for respiratory support, with venovenous (VV) configuration utilized in 91%

of patients. However, given the myriad cardiac complications also seen with the infection, there may be a greater role for venoarterial (VA) or combination (e.g., veno-venoarterial) modes, currently comprising <5% of cases.[81]

Data on outcomes for COVID patients placed on ECMO are limited and widely variable. A systematic review of primarily VV ECMO patients reported survival rates from 1.4% to 48.3% with an overall reported mortality of 19.83%.[82] Beyond mortality, ECMO carries a significant risk of complications including, but not limited to, vascular complications, stroke, hemorrhage, infection, limb ischemia, and renal failure.[83] Patient selection for such a high risk and resource-intensive therapy is challenging, a decision that is only amplified in the midst of a pandemic in which resources are already stretched.[84] The use of ECMO for COVID-19 patients with concurrent cardiovascular and respiratory failure is even more strongly debated, as initial recommendations advised limiting the technology's use to patients with single organ failure and the highest probability of survival.[85] Of note, while the "SAVE" – Survival After Veno-arterial ECMO – Score was developed to identify predictors of survival for patients receiving ECMO for refractory cardiogenic shock, no scoring system has yet been prospectively validated for patients with COVID-19.[86]

ECMO is likely to comprise a small subset of therapies utilized in the care of COVID-19 patients, and its use for patients with combined respiratory and cardiac failure should be reserved for experienced centers only after careful consideration of resource availability and likelihood of benefit.

Conclusion

While much attention is paid to the pulmonary injury associated with COVID-19, cardiovascular sequelae can significantly increase the risk of morbidity and mortality, particularly in critically ill patients with SARS-CoV2. The precise mechanism of cardiac injury remains elusive and is likely due to a combination of factors including direct myocardial damage and indirect inflammatory-mediated effects. Clinically, patients may develop a multitude of cardiac complications with the most serious being cor pulmonale and symptomatic pulmonary embolism. A standardized approach to routine POCUS and TTE may aid in early identification and guide critical care therapies including vasopressors and inhaled agents. A number of therapies are available to support the failing heart in SARS-CoV-2 infection, but more data is needed to identify the optimal therapeutic approach.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization. Available from: https://covid19.who.int/. [Last accessed on 2020 Sep 16].
2. Deng G, Yin M, Chen X, Zeng F. Clinical determinants for fatality of 44,672 patients with COVID-19. Crit Care 2020;24:179.
3. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323:1775-6.
4. Gémes K, Talbäck M, Modig K, Ahlbom A, Berglund A, Feychting M, *et al*. Burden and prevalence of prognostic factors for severe COVID-19 in Sweden. Eur J Epidemiol 2020;35:401-9.
5. Li X, Pan X, Li Y, An N, Xing Y, Yang F, *et al*. Cardiac injury associated with severe disease or ICU admission and death in hospitalized patients with COVID-19: A meta-analysis and systematic review. Crit Care 2020;24:468.
6. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-80.e8.
7. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. Am J Respir Crit Care Med 2020;202:756-9.
8. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res 2020;116:1097-100.
9. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, *et al*. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: A case series. Lancet 2020;396:320-32.
10. Liu F, Li L, Xu M, Wu J, Luo D, Zhu YS, *et al*. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol 2020;127:104370.
11. Prabhu SD. Cytokine-induced modulation of cardiac function. Circ Res 2004;95:1140-53.
12. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31.
13. Levi M, van der Poll T, Büller HR. Bidirectional relation between inflammation and coagulation. Circulation 2004;109:2698-704.
14. Ryan D, Frohlich S, McLoughlin P. Pulmonary vascular dysfunction in ARDS. Ann Intensive Care 2014;4:28.
15. Crystal GJ, Pagel PS. Right ventricular perfusion: Physiology and clinical implications. Anesthesiology 2018;128:202-18.
16. Park JF, Banerjee S, Umar S. In the eye of the storm: The right ventricle in COVID-19. Pulm Circ 2020;10:1-7.
17. Zochios V, Parhar K, Tunnicliffe W, Roscoe A, Gao F. The right ventricle in ARDS. Chest 2017;152:181-93.
18. Li Y, Li H, Zhu S, Xie Y, Wang B, He L, *et al*. Prognostic value of right ventricular longitudinal strain in patients With COVID-19. JACC Cardiovasc Imaging 2020;13:2287-99.
19. Whittenberger JL, McGregor M, Berglund E, Borst HG. Influence of state of inflation of the lung on pulmonary vascular resistance. J Appl Physiol 1960;15:878-82.
20. Niden AH. The acute effects of atelectasis on the pulmonary circulation. J Clin Invest 1964;43:810-24.
21. Jardin F, Brun-Ney D, Hardy A, Aegerter P, Beauchet A, Bourdarias JP. Combined thermodilution and two-dimensional echocardiographic evaluation of right ventricular function during respiratory support with PEEP. Chest 1991;99:162-8.
22. Dambrosio M, Fiore G, Brienza N, Cinnella G, Marucci M, Ranieri VM, *et al*. Right ventricular myocardial function in ARF patients. PEEP as a challenge for the right heart. Intensive Care Med 1996;22:772-80.
23. Luecke T, Pelosi P. Clinical review: Positive end-expiratory pressure and cardiac output. Crit Care 2005;9:607-21.
24. Jardin F, Vieillard-Baron A. Is there a safe plateau pressure in ARDS? The right heart only knows. Intensive Care Med 2007;33:444-7.
25. Mekontso Dessap A, Boissier F, Charron C, Bégot E, Repessé X, Legras A, *et al*. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: Prevalence, predictors, and clinical impact. Intensive Care Med 2016;42:862-70.
26. Potus F, Mai V, Lebret M, Malenfant S, Breton-Gagnon E, Lajoie AC, *et al*. Novel insights on the pulmonary vascular consequences of COVID-19. Am J Physiol Lung Cell Mol Physiol 2020;319:L277-L288.
27. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, *et al*. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120-8.

28. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-7.
29. Becattini C, Casazza F, Forgione C, Porro F, Fadin BM, Stucchi A, *et al*. Acute pulmonary embolism: External validation of an integrated risk stratification model. Chest 2013;144:1539-45.
30. Creel-Bulos C, Hockstein M, Amin N, Melhem S, Truong A, Sharifpour M. Acute Cor Pulmonale in Critically Ill Patients with Covid-19. N Engl J Med 2020;382:e70.
31. Benzakoun J, Hmeydia G, Delabarde T, Hamza L, Meder JF, Ludes B, *et al*. Excess out-of-hospital deaths during the COVID-19 outbreak: Evidence of pulmonary embolism as a main determinant. Eur J Heart Fail 2020;22:1046-7.
32. Ali S, Mathew S, Pappachan JM. Acute cor pulmonale from saddle pulmonary embolism in a patient with previous COVID-19: Should we prolong prophylactic anticoagulation? Int J Infect Dis 2020;97:299-302.
33. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. Eur Heart J 2020;42:206.
34. Kim IC, Kim JK, Kim HA, San H. COVID-19-related myocarditis in a 21-year-old female patient. Eur Heart J 2020;41:1859.
35. Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, *et al*. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J 2020;41:1861-2.
36. Kariyanna PT, Sutarjono B, Grewal E, Singh KP, Aurora L, Smith L, *et al*. A systematic review of COVID-19 and myocarditis. Am J Med Case Rep 2020;8:299-305.
37. Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, *et al*. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020;17:1463-71.
38. Pirzada A, Mokhtar AT, Moeller AD. COVID-19 and myocarditis: What do we know so far? CJC Open 2020;2:278-85.
39. Cheng P, Zhu H, Witteles RM, Wu JC, Quertermous T, Wu SM, *et al*. Cardiovascular risks in patients with COVID-19: Potential mechanisms and areas of uncertainty. Curr Cardiol Rep 2020;22:34.
40. Tsao CW, Strom JB, Chang JD, Manning WJ. COVID-19-associated stress (takotsubo) cardiomyopathy. Circ Cardiovasc Imaging 2020;13:e011222.
41. Minhas AS, Scheel P, Garibaldi B, Liu G, Horton M, Jennings M, *et al*. Takotsubo syndrome in the setting of COVID-19. JACC Case Rep 2020;2:1321-5.
42. Pasqualetto MC, Secco E, Nizzetto M, Scevola M, Altafini L, Cester A, *et al*. Stress cardiomyopathy in COVID-19 disease. Eur J Case Rep Intern Med 2020;7:001718.
43. Giustino G, Croft LB, Oates CP, Rahman K, Lerakis S, Reddy VY, *et al*. Takotsubo cardiomyopathy in COVID-19. J Am Coll Cardiol 2020;76:628-9.
44. Desai HD, Jadeja DM, Sharma K. Takotsubo syndrome a rare entity in patients with COVID-19: An updated review of case-reports and case-series. Int J Cardiol Heart Vasc 2020;29:100604.
45. Jabri A, Kalra A, Kumar A, Alameh A, Adroja S, Bashir H, *et al*. Incidence of stress cardiomyopathy during the coronavirus disease 2019 pandemic. JAMA Netw Open 2020;3:e2014780.
46. Delmas C, Bouisset F, Lairez O. COVID-19 pandemic: No increase of takotsubo syndrome occurrence despite high-stress conditions. ESC Heart Fail 2020;7:2143-5.
47. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
48. Sala S, Peretto G, De Luca G, Farina N, Campochiaro C, Tresoldi M, *et al*. Low prevalence of arrhythmias in clinically stable COVID-19 patients. Pacing Clin Electrophysiol 2020;43:891-3.
49. Bhatla A, Mayer MM, Adusumalli S, Hyman MC, Oh E, Tierney A, *et al*. COVID-19 and cardiac arrhythmias. Heart Rhythm 2020;17:1439-44.
50. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review. Heart Rhythm 2020;17:1472-9.
51. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, *et al*. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:1036-41.
52. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, *et al*. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: Open label, randomised controlled trial. BMJ 2020;369:m1849.
53. Magagnoli J, Narendran S, Periera F, Cummings TH, Hardin JW, Sutton SS, *et al*. Outcomes of hydroxychloroquine usage in united states veterans hospitalized with COVID-19. Med (N Y) 2020;1:114-27.e3.
54. Misra S, Nath M, Hadda V, Vibha D. Efficacy of various treatment modalities for nCOV-2019: A systematic review and meta-analysis. Eur J Clin Invest 2020;50:e13383.
55. Hall DP, Jordan H, Alam S, Gillies MA. The impact of focused echocardiography using the Focused Intensive Care Echo protocol on the management of critically ill patients, and comparison with full echocardiographic studies by BSE-accredited sonographers. J Intensive Care Soc 2017;18:206-11.
56. Jain SS, Liu Q, Raikhelkar J, Fried J, Elias P, Poterucha TJ, *et al*. Indications for and Findings on Transthoracic Echocardiography in COVID-19. J Am Soc Echocardiogr 2020;33:1278-84.
57. Huang G, Vengerovsky A, Morris A, Town J, Carlbom D, Kwon Y. Development of a COVID-19 point-of-care ultrasound protocol. J Am Soc Echocardiogr 2020;33:903-5.
58. Anile A, Castiglione G, Zangara C, Calabro C, Vaccaro M, Sorbello M. COVID: The new ultrasound alphabet in SARS-CoV-2 era. Anesth Analg 2020;131:e232-e234.
59. Johri AM, Galen B, Kirkpatrick JN, Lanspa M, Mulvagh S, Thamman R. ASE statement on point-of-care ultrasound during the 2019 novel coronavirus pandemic. J Am Soc Echocardiogr 2020;33:670-3.
60. Kirkpatrick JN, Mitchell C, Taub C, Kort S, Hung J, Swaminathan M. ASE statement on protection of patients and echocardiography service providers during the 2019 novel coronavirus outbreak: Endorsed by the American College of Cardiology. J Am Soc Echocardiogr 2020;33:648-53.
61. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, *et al*. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
62. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. Chest 2007;132:1440-6.
63. Bloomfield R, Noble DW, Sudlow A. Prone position for acute respiratory failure in adults. Cochrane Database Syst Rev 2015:CD008095.
64. Keyaerts E, Vijgen L, Chen L, Maes P, Hedenstierna G, Van Ranst M. Inhibition of SARS-coronavirus infection *in vitro* by S-nitroso-N-acetylpenicillamine, a nitric oxide donor compound. Int J Infect Dis 2004;8:223-6.
65. Gebisstorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev 2016:CD002787.
66. Fuller BM, Mohr NM, Skrupky L, Fowler S, Kollef MH, Carpenter CR. The use of inhaled prostaglandins in patients with ARDS: A systematic review and meta-analysis. Chest 2015;147:1510-22.
67. Chen L, Liu P, Gao H, Chao D, Wang F, Zhu Y, *et al*. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: A rescue trial in Beijing. Clin Infect Dis 2004;39:1531-5.
68. Parikh R, Wilson C, Weinberg J, Gavin D, Murphy J, Reardon CC. Inhaled nitric oxide treatment in spontaneously breathing COVID-19 patients. Ther Adv Respir Dis. 2020;14:1753466620933510. doi:10.1177/1753466620933510.
69. Cardinale M, Esnault P, Cotte J, Cungi PJ, Goutorbe P. Effect of almitrine bismesylate and inhaled nitric oxide on oxygenation in COVID-19 acute respiratory distress syndrome. Anaesth Crit Care Pain Med 2020;39:471-2.
70. Tavazzi G, Marco P, Mongodi S, Dammassa V, Romito G, Mojoli F. Inhaled nitric oxide in patients admitted to intensive care unit with COVID-19 pneumonia. Crit Care 2020;24:508.

71. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
72. Hu Y, Sun J, Dai Z, Deng H, Li X, Huang Q, *et al*. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Virol 2020;127:104371.
73. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, *et al*. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: A prospective cohort study. Lancet 2020;395:1763-70.
74. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
75. Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, *et al*. Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. Lancet Respir Med 2020;8:506-17.
76. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, *et al*. Surviving sepsis campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med 2020;46:854-87.
77. Michard F, Malbrain ML, Martin GS, Fumeaux T, Lobo S, Gonzalez F, *et al*. Haemodynamic monitoring and management in COVID-19 intensive care patients: An International survey. Anaesth Crit Care Pain Med 2020;39:563-9.
78. Peek GJ, Mugford M, Tiruvoopati R, Wilson A, Allen E, Thalanany MM *et al*. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicenter randomized controlled trial. Lancet 2009;374:1351-63.
79. Extracorporeal Life Support Organization, International Summary. Available from: https://www.elso.org/Registry/Statistics/InternationalSummary.aspx. [Last accessed on 2020 Sep 16].
80. Extracorporeal Life Support Organization, COVID-19 Registry. Available from: https://www.elso.org/Registry/FullCOVID19RegistryDashboard.aspx. [Last accessed on 2020 Sep 16].
81. De Piero ME, Lo Coco V, Taccone FS, Belliato M, Broman LM, Malfertheiner MV, *et al*. Has venoarterial ECMO been underutilized in COVID-19 patients? Innovations (Phila) 2020;15:317-21.
82. Haiduc AA, Alom S, Melamed N, Harky A. Role of extracorporeal membrane oxygenation in COVID-19: A systematic review. J Card Surg 2020;35:2679-87.
83. Kaushal M, Schwartz J, Gupta N, Im J, Leff J, Jakobleff WA, *et al*. Patient demographics and extracorporeal membranous oxygenation (ECMO)-related complications associated with survival to discharge or 30-day survival in adult patients receiving venoarterial (VA) and venovenous (VV) ECMO in a Quaternary Care Urban Center. J Cardiothorac Vasc Anesth 2019;33:910-7.
84. Prekker ME, Brunsvold ME, Bohman JK, Fischer G, Gram KL, Litell JM, *et al*. Regional planning for extracorporeal membrane oxygenation allocation during coronavirus disease 2019. Chest 2020;158:603-7.
85. Rajagopal K, Keller SP, Akkanti B, Bime C, Loyalka P, Cheema FH, *et al*. Advanced pulmonary and cardiac support of COVID-19 patients: Emerging recommendations from ASAIO – A "Living Working Document". ASAIO J 2020;66:588-98.
86. Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, *et al*. Predicting survival after ECMO for refractory cardiogenic shock: The survival after veno-arterial-ECMO (SAVE)-score. Eur Heart J 2015;36:2246-56.