Malignant ventricular arrhythmias in patients with severe acute respiratory distress syndrome due to COVID-19 without significant structural heart disease

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Introduction

Since December 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has resulted in a pandemic of novel coronavirus (COVID-19) infections. Although predominantly a respiratory illness that can cause acute respiratory distress syndrome (ARDS), data suggest cardiovascular involvement contributes significantly to the disease's mortality. Data from Wuhan, China, demonstrated patients with pre-existing cardiovascular disease and elevated troponin levels had 69.44% mortality.[1]

ARDS is defined by acute hypoxemic respiratory failure of noncardiac etiology, bilateral pulmonary infiltrates, and a decreased PaO2/FIO2 ratio with mortality rates reaching 40%.[2] After decades of ARDS research, little has been described about any associated ventricular arrhythmias despite the potential interplay between pulmonary pathology, treatments, and malignant arrhythmias.

Although significant structural heart disease is a risk factor for ventricular arrhythmias, their occurrence in the absence of major cardiac abnormalities requires a full examination of cardiac and noncardiac causes. Furthermore, since respiratory failure is typically associated with pulseless electrical activity (PEA) and asystole rather than ventricular tachycardia (VT) or ventricular fibrillation (VF), the etiology of malignant ventricular arrhythmias in patients without heart disease and a primarily acute pulmonary disease process requires further investigation.[3] We present a series of COVID-19-infected patients with preserved cardiac function who developed ARDS and refractory ventricular arrhythmias. To the best of our knowledge, this represents the first report of VT or VF as the primary cause of death in COVID-19 patients without previous evidence of significant structural heart disease. We obtained Institutional Review Board approval to collect data on patient characteristics and frequently monitored tests in ARDS and severe COVID-19 infection to examine similarities and differences in acid-base status, electrolytes, troponin, inflammatory biomarkers, intubation status, and renal function (Table 1). Electrocardiogram (ECG) data were also collected along with use of proarrhythmic medications (Table 2).

KEY TEACHING POINTS

- Myocardial injury is defined by elevated serum troponin levels and is associated with increased mortality in novel coronavirus (COVID-19) infection.
- Current practice recommendations for management of acute respiratory distress syndrome, a common process in severely infected COVID-19 patients, encourage a strategy of lung-protective ventilation. This includes low tidal volume ventilation to prevent ventilator-associated barotrauma and oxygen toxicity, permissive hypercapnia/acidosis, and lower oxygenation goals.
- A lung-protective ventilation strategy in COVID-19 patients where renal failure, metabolic acidosis, and hyperkalemia are common may predispose certain patients with myocardial injury to malignant ventricular arrhythmias.

Case report

Case 1

A 32-year-old man with morbid obesity and hypertension presented with malaise and dyspnea. Upon presentation, he

KEYWORDS Acute respiratory distress syndrome; Arrhythmia; COVID-19; Ventricular fibrillation; Ventricular tachycardia
(Heart Rhythm Case Reports 2020;6:858–862)

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Conflicts of Interest: None of the authors have any conflicts of interest to disclose. **Address reprint requests and correspondence:** Dr Jose M. Dizon, Department of Medicine, Division of Cardiology, New York Presbyterian Hospital, Columbia University Irving Medical Center, 177 Fort Washington Ave, 5th Floor, Suite 435F, New York, NY 10032. E-mail address: jmd11@cumc.columbia.edu.

https://doi.org/10.1016/j.hrcr.2020.08.017

Table 1 Patient characteristics and prearrest laboratory findings

Case	Patient age (years)	Sex	BMI	Medical history	LV	RV	Intubated	pH	pCO2 (mm Hg)	Lactate (normal 0.5–1.6 mmol/L)	K+ (normal 3.5–5.1 mmol/L)	Mg (normal 1.6–2.4 mg/dL)	eGFR (normal ≥60 mL/min/1.73 m^2)	hsTpnT (normal ≤22 ng/L)	Ferritin (normal 30–400 ng/mL)	IL-6 (normal ≤5.0 pg/mL)	ESR (normal 0–15 mm/h)	CRP (normal 0–10 mg/L)	WBC (normal 3.12–8.44 x 1000/μL)
1	32	M	55.0	Hypertension	>55%	Mildly increased	Y	7.30 (arterial)	44 (arterial)	2.5	6.1	3.2	CRRT	621	17,320	14	73	186.89	25.46
2	39	M	34.1	Hypertension Diabetes Epilepsy	Normal	ND	Y	7.19 (arterial)	49.7 (arterial)	1.8	5.0	1.7	53	20	4178	167	61	ND	3.7
3	64	M	30.3	Hypertension Diabetes	ND	ND	Y	7.23 (arterial)	43 (arterial)	2.1	6.2	3.2	22	29	2507	108.4	123	>300	6.62
4	43	M	49.7	Hypertension Asthma	Grossly normal	Increased size Reduced function	Y	7.23 (arterial)	48 (arterial)	2.6	6.6	2.7	CRRT	132	9158	59	>130	>300	16.15
5	64	M	32.0	CAD with stent Diabetes Alcohol abuse	60%–65%	ND	Y	7.29 (venous)	58 (venous)	3.3 (venous, normal 0.5–2.2 mmol/L)	5.0	4.2	41	32	2355	ND	101	110.21	9.8

BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; CRRT = continuous renal replacement therapy; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; hsTpnT = high-sensitivity troponin T; K+ = potassium level; LV = left ventricle; Mg = magnesium level; ND = not documented; RV = right ventricle; WBC = white blood cell; Y = yes.

was febrile (38.1°C) with an oxygen saturation of 68% on room air and was emergently intubated. The initial ECG revealed sinus rhythm with a prolonged QTc (Bazett) of 480 ms and nonspecific T-wave changes (Supplemental Figure 1A). Initial blood work showed elevated troponin, creatinine, and inflammatory markers. A SARS-CoV-2 RT-PCR nasal swab was positive. He received hydroxychloroquine, azithromycin, and sarilumab as part of a clinical trial and completed his course without further QT prolongation. Despite intubation, he had refractory hypoxia treated with inhaled nitric oxide, paralysis, and proning. He developed shock and renal failure, requiring continuous renal replacement therapy. In accordance with ARDS ventilator protocols, his pH was 7.2–7.3 resulting from a mixed respiratory and metabolic acidosis. The patient was hyperkalemic (5.0–7.0 mmol/L) in the 24 hours leading up to his arrest, despite dialysis. The final 12-lead ECG showed a rightward axis shift, prolonged PR interval, peaked T waves compared to prior, and a QT/QTc (Bazett) of 304/447 ms (Supplemental Figure 1B).

His hs-TpnT rose (76 to 422 ng/L) leading up to his arrest. Echocardiogram revealed normal left ventricular (LV) function and mildly reduced right ventricular function. He later developed polymorphic VT, was defibrillated 3 times, and received amiodarone. After a brief return of spontaneous circulation, he developed PEA and was unable to be resuscitated. He died 10 days after admission.

Case 2

A 39-year-old man with hypertension, non-insulin-dependent diabetes, and epilepsy presented with fever, cough, and dyspnea. Upon presentation, his temperature was 39.4°C with an oxygen saturation of 85% on room air that increased to 95% on 6 liters of oxygen delivered by nasal cannula. Laboratory evaluation showed a normal troponin, elevated inflammatory markers, and a positive SARS-CoV-2 RT-PCR nasal swab. ECG demonstrated sinus rhythm with nonspecific T-wave changes and a QT/QTc of 420/440 ms (Supplemental Figure 2). An echocardiogram revealed normal LV function. He received hydroxychloroquine and azithromycin and was intubated for worsening hypoxia. With lung protective ventilation, his oxygen saturation improved to 88%–100% with a pH of 7.33. The following day, the patient self-extubated and was emergently reintubated without complications or immediate resultant change in clinical status. One day later, he became febrile and hypotensive, requiring vasopressor support. He developed pulseless monomorphic VT. Advanced care life support and cardiopulmonary resuscitation (CPR) were initiated with 2 attempted defibrillations. He briefly returned to sinus rhythm, but then degenerated to VF and died 3 days after admission.

Case 3

A 64-year-old man with hypertension and insulin-dependent diabetes presented with malaise, cough, chills, and dyspnea. He had no clinical history to indicate heart failure. On

Table 2 Prearrest electrocardiographic characteristics and contributors

Case	Rhythm	Rate (beats/min)	Intervals (ms)	ST/T-wave changes	Pressors	Antiarrhythmics	QT-prolonging drugs
1	Sinus tachycardia	130	PR – 148 QRSd – 102 QT – 304 QTc – 447	Peaked T waves	None	Metoprolol	Chlordiazepoxide Hydromorphone
2	Sinus rhythm	66	PR – 142 QRSd – 92 QT – 420 QTc – 440	Nonspecific	None	None	Hydroxychloroquine Azithromycin Hydromorphone
3	Sinus rhythm	99	PR – 138 QRSd – 78 QT – 344 QTc – 441	None	Norepinephrine Vasopressin	None	Hydroxychloroquine Chlordiazepoxide Hydromorphone
4	Sinus tachycardia	107	PR – 154 QRSd – 90 QT – 338 QTc – 451	None	Epinephrine Norepinephrine Vasopressin	Amiodarone	Hydroxychloroquine Azithromycin
5	Sinus rhythm	90	PR – 122 QRSd – 82 QT – 394 QTc – 481	Lateral ST depressions	None	None	None

presentation, his temperature was 39.4°C and his oxygen saturation was 50% on room air, which improved to 94% on non-rebreather mask. ECG demonstrated borderline sinus tachycardia with a premature ventricular complex and a QT/QTc of 344/441 ms, but no evidence of ischemia or prior infarct (Supplemental Figure 3). Laboratory evaluation showed elevated troponin, creatinine, and inflammatory markers. A SARS-CoV-2 RT-PCR was positive and he received hydroxychloroquine, azithromycin, and tocilizumab. He became progressively hypoxic, requiring intubation on hospital day 3, and was managed using ARDS ventilator protocols. He developed renal failure and shock, requiring vasopressor support. In the 24 hours prior to his arrest, his pH ranged from 7.23 to 7.27 with potassium levels of 6.2–6.4 mmol/L. He also progressed into diabetic ketoacidosis. Despite improving clinically, he developed polymorphic VT without prolonged QT on telemetry. CPR and defibrillation were unsuccessful and the patient died 5 days after admission.

Case 4

A 43-year-old man with hypertension and asthma presented with cough, chills, and dyspnea. A SARS-CoV-2 RT-PCR nasal swab was positive. After admission, he required intubation for worsening hypoxia despite a non-rebreather mask with a PaO2:FIO2 ratio of 100. In line with ARDS protocols, permissive hypercapnia was present (pCO2 48–57 mm Hg) with pH values of 7.22–7.23. His oxygenation improved, but vasopressors were required for hemodynamic support. He developed acute renal failure requiring continuous renal replacement therapy, but had persistent hyperkalemia (6.4–6.7 mmol/L). His baseline ECG was sinus tachycardia with a left anterior fascicular block, normal intervals, and no evidence of ischemia or infarct (Supplemental Figure 4A). He received hydroxychloroquine, azithromycin, and tocilizumab. He also later received intravenous amiodarone for paroxysmal atrial flutter that resolved (Supplemental Figure 4B). An echocardiogram demonstrated grossly normal LV function. On the ECG recorded most proximate to death, his QT/QTc was 338/451 ms. On the day he died, he had pH of 7.23, potassium of 6.6 mmol/L, hs-TpnT of 132 ng/L, and elevated inflammatory markers. He developed pulseless VT, which was treated with a single electrical cardioversion. CPR was provided, but there was no longer a shockable rhythm. The patient died 3 days after presentation.

Case 5

A 64-year-old man with obesity, non-insulin-dependent diabetes, coronary artery disease with a stent placed to the obtuse marginal branch in 2018 in the setting of unstable angina, and alcohol abuse presented with cough, dyspnea, and hyperglycemia. On arrival, his oxygenation was 88% on room air. His serum glucose was 770 mg/dL and ketones were present. A venous blood gas revealed a pH of 7.29 with a pCO2 of 58 mm Hg, consistent with a mixed acidosis. Other blood work demonstrated reduced renal function, elevated troponin, and elevated inflammatory markers. A SARS-CoV-2 RT-PCR nasal swab was positive. ECG showed sinus rhythm with premature supraventricular complexes, nonspecific lateral ST depressions unchanged from prior ECGs, normal intervals except a QT/QTc of 394/481 ms, and no evidence of prior infarct (Supplemental Figure 5). He was on no QT-prolonging medications. LV function was 60%–65% when last assessed by ventriculography in 2018. He required intubation, which was thought to be esophageal when his oxygenation remained 75%. On

repositioning the endotracheal tube, the patient developed sinus bradycardia and subsequently VF. Advanced care life support and CPR were provided, including 150 mg of intravenous amiodarone and 2 unsuccessful attempts at defibrillation. The patient developed asystole and died 1 day after admission.

Discussion

Ventricular arrhythmias are more common in patients with structural heart disease. Likewise, critically ill patients have a higher incidence of ventricular arrhythmias.[4] Data suggest cardiac arrest rates as high as 11.8% in intensive care unit patients with pneumonia, who frequently have many medical comorbidities.[5] However, the incidence of malignant ventricular arrhythmias as opposed to PEA or asystole in patients with ARDS is poorly defined and has yet to be reported in COVID-19.

In a study from Wuhan City, China, 5.9% of COVID-19 patients developed VT or VF, increasing to 11.5% in those with myocardial injury.[1] Another analysis of cardiac arrest rhythms reported asystole in 89.7%, PEA in 4.4%, and a shockable rhythm in 5.9%, consistent with predominantly respiratory arrest.[6] Detailed analyses of the arrhythmias and clinical data in these studies were not reported.

We present 5 patients among whom cardiac risk factors were common, including obesity, hypertension, and diabetes. All patients were male, which has been associated with increased mortality in COVID-19.[6] Only 1 patient (case 5) had a history of coronary artery disease, but none had a history of heart failure, LV dysfunction, or ECG evidence of infarct. However, all had VT or VF, which was refractory to defibrillation and amiodarone in 3 patients (cases 1, 2, and 5). Although these patients share several things in common with historical critically ill patients, we postulate that there are unique pathophysiologic and iatrogenic contributors to malignant arrhythmias in the management of ARDS from COVID-19.

Medications under investigation to treat COVID-19 infection known to cause QT prolongation, such as hydroxychloroquine and azithromycin, were used in a majority of our patients (cases 1, 2, 3, and 4). Although these medications are known to prolong QT interval, only 1 of our patients (case 5) had a borderline prolonged QTc prior to arrest and he had not received any QT-prolonging medications.

Hypercoagulability is a unique manifestation of severe COVID-19 disease.[7] Although we could not exclude pulmonary embolism contributing to mortality, hypoxic/respiratory deaths typically cause pulseless electrical activity or asystole. Furthermore, they did not have acutely worsened hypoxia or evidence of severe right ventricular dysfunction.

Studies from the ARDS Network database recommend permissive hypercapnia, allowing pH values down to approximately 7.20 in order to prioritize low tidal volume ventilation to avoid barotrauma, tolerating mild hypoxemia with target PaO2 levels of 55–80 mm Hg to avoid oxygen toxicity.[8] Although pulmonary benefits have been established, little data exist on the adverse cardiac effects of the resultant acidosis and tissue hypoxia. The concomitant metabolic acidosis from renal failure and/or lactatemia seen in all of our patients could further complicate acid-base goals.

On a cellular level, acidosis results in extrusion of potassium ions. Hyperkalemia results in slowed conduction, which can predispose myocardium for reentrant arrhythmias.[9] Hyperkalemia, acidosis, and hypoxia—all of which are systemically present in severe ARDS patients—have been suggested to promote ventricular arrhythmias.[10]

Myocardial injury has been described in 7.2%–27.8% of patients with severe COVID-19.[1] Although acute ischemia is possible, myocarditis is more likely responsible for this finding in COVID-19 patients and may result from direct viral infection, cytokine storm, or hypoxia.[11,12] Four out of 5 patients (cases 1, 3, 4, and 5) had elevated high-sensitivity troponin levels, indicating myocardial damage. One patient (case 5) had nonspecific ST-segment depressions that were unchanged from past ECGs in our medical records, but the others did not exhibit any ischemic ECG changes. Silent ischemia cannot be excluded, but myocarditis was likely, given our current understanding of cardiac involvement in COVID-19.

We postulate that acidosis and hyperkalemia from metabolic stressors including liberalized ARDS management goals coupled with an inflamed myocardium contributed to VT/VF. As protocols are developed to manage COVID-19-related ARDS, strategies to optimize acid-base and electrolyte balance should be incorporated.

Limitations

Individually, not all patients had cardiac function assessments prior to their demise owing to attempts to limit personnel exposure to COVID-19-infected patients to that which was absolutely necessary for clinical care. However, 3 patients (cases 1, 2, and 4) had echocardiograms during admission, another (case 5) had one recently, and the last (case 3) had no evidence of ischemia or infarct on ECG. None had any clinical heart failure prior to admission. The cause of death was performed through review of medical records and interviews with the physicians present during the arrests, as ECGs and telemetry of the tachyarrhythmias were not available. Finally, since this study is a retrospective case series, our hypotheses, although based on electrophysiologic principles, are still speculative.

Conclusions

In our series of 5 patients with ARDS in the setting of severe COVID-19 infection who died of ventricular arrhythmias despite normal baseline cardiac function, we postulate that iatrogenic factors of permissive hypercapnia/acidosis related to ARDS management and commonly encountered hyperkalemia may potentially be hazardous to some patients with myocardial involvement of COVID-19 infection. Studies should focus on optimization of management protocols to take into account cardiac vulnerabilities, as well as attempts

to mitigate known risk factors for ventricular arrhythmias among COVID-19-infected patients.

Acknowledgments

The authors wish to acknowledge the heroic dedication of the nurses, support staff, physicians, and all other front-line workers at our institution and elsewhere throughout the COVID-19 pandemic putting themselves at risk to help others in need.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://10.1016/j.hrcr.2020.08.017.

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