Coronavirus Disease 2019 Infection in Children with Pre-Existing Heart Disease

Megan Simpson, DO[1], Catherine Collins, MD[2], Dustin B. Nash, MD[3], Laurie E. Panesar, MD[4], and Matthew E. Oster, MD, MPH[1,5]

We present 7 children with congenital heart disease and coronavirus disease 2019. Of these, 5 were younger than 1 year of age and 3 had atrioventricular canal defect and trisomy 21. All 7 developed acute decompensation, with 1 death in an 18-year-old with hypertrophic cardiomyopathy and other comorbidities. *(J Pediatr 2020;227:302-7).*

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel virus causing the coronavirus disease 2019 (COVID-19) pandemic. Much is unknown about its clinical course and management, particularly among children with pre-existing cardiac conditions. In adults, COVID-19 has associated cardiac manifestations including heart failure, cardiogenic shock, acute myocardial injury, and arrhythmia and is associated with increased mortality.[1] We share our early multicenter experience with children admitted from March 27, 2020, to April 27, 2020, with a history of congenital heart disease who were hospitalized with COVID-19 as diagnosed by SARS-CoV-2 polymerase chain reaction (PCR). The pertinent details for each case are summarized in the **Table**.

Case 1

An ex-35-week, 3-month-old male patient with trisomy 21 and unrepaired complete atrioventricular canal (CAVC) defect with marginally compensated heart failure on maximal medical therapy of furosemide, chlorothiazide, and digoxin presented with tachycardia, tachypnea, and hypoxemia in the setting of 2 days of fever and irritability. His chest radiograph (CXR) was concerning for bilateral scattered atelectasis and hyperinflation. Venous blood gas demonstrated hypercarbia of 51 mm Hg. He was SARS-CoV-2 positive by PCR on admission. He had no known sick contacts.

He was given broad-spectrum antibiotics for 24 hours. He required up to 8 L of high-flow nasal cannula of respiratory support and was weaned off respiratory support on hospital day 4. He was discharged on hospital day 6.

AKI	Acute kidney injury
AV	Atrioventricular
BNP	Brain natriuretic peptide
CAVC	Complete atrioventricular canal
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CXR	Chest radiograph
ECMO	Extracorporeal membrane oxygenation
PCR	Polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2

He remained stable as an outpatient until his planned readmission 4 weeks after discharge for complete surgical repair. One week after his surgical repair, he had hypercarbic respiratory failure of unclear etiology. Postoperative catheterization was notable for a mildly elevated pulmonary vascular resistance with a pulmonary blood flow to systemic blood flow ratio of 1.7:1 in the setting of a residual ventricular septal defect. He subsequently had his ventricular septal defect closed and was discharged home on overnight oxygen and sildenafil. At 95 days after initial discharge, he remained stable as an outpatient.

Case 2

A 3-month-old female patient with trisomy 21 and unrepaired CAVC defect with compensated heart failure maintained on furosemide, spironolactone, and carvedilol presented with respiratory distress and hypoxemia. Her CXR was concerning for pneumonia and pulmonary edema (**Figure 1**; available at www.jpeds.com). Echocardiogram at baseline showed mild-to-moderate common atrioventricular (AV) valve regurgitation with mildly dilated and hypertrophied right ventricle. Echocardiogram after admission showed severe left AV valve regurgitation, otherwise stable. She had an elevated brain natriuretic peptide (BNP) and C-reactive protein (CRP). On admission, a standard respiratory viral panel was negative. SARS-CoV-2 PCR testing sent on hospital day 13 using the respiratory viral sample obtained on admission was positive. She had no known sick contacts.

She was diagnosed with worsening heart failure with acute respiratory failure and required aggressive diuresis, milrinone, and mechanical ventilation. A dexmedetomidine infusion was started due to persistent narrow-complex

From the [1]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA; [2]Department of Cardiology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; [3]Division of Cardiology, Children's Hospital of Philadelphia, Philadelphia; PA; [4]Department of Cardiology, Stony Brook Children's Hospital, Stony Brook, NY; and [5]Sibley Heart Center Cardiology, Children's Healthcare of Atlanta, Atlanta, GA

The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.07.069

Table. Characteristics, clinical management, and outcomes of children with COVID-19 and congenital heart disease

Case nos.	Age	Cardiac history	Presenting signs and symptoms	Key CXR findings	Key echocardiography findings	BNP, pg/mL	Troponin, ng/mL	Maximum CRP, mg/dL	Maximum respiratory support	Milrinone, yes/no	ECMO	COVID-19 treatment	Days in ICU	Days on ward	Outcome
Case 1	3 mo	CAVC	Fever, irritability, hypoxemia, tachypnea, tachycardia	Hyperinflated lungs with scattered atelectasis; no focal consolidation	Not performed	77	Not performed	2	8 L HFNC FiO_2 21%	No	None	None	4	2	Recovery, discharged home. Readmitted for complete surgical repair, discharged home
Case 2	3 mo	CAVC	Increased work of breathing, decreased oral intake, hypoxemia	Diffuse interstitial densities and increased pulmonary vascularity with superimposed linear areas of airspace opacity at the bilateral lung bases and in the upper lobes, cardiomegaly	Moderate-to-severe regurgitation from left AV-valve component on common AV- valve; trivial regurgitation from right component. Mild-to-moderately hypertrophied and dilated right ventricle.	530	Not performed	7.7	MV PRVC mode, rate 37 bpm, TV 27 mL, PEEP 7 cmH_2O, PS +10 cmH_2O, PIPs in the 20s cmH_2O, FiO_2 60%	Yes	None	Remdesivir, convalescent plasma	100	9, ongoing	Improved after complete surgical repair, remains inpatient
Case 3	6 mo	ALCAPA	Fever, increased work of breathing, decreased oral intake, hypoxemia	Cardiomegaly with ground-glass opacities consistent with pneumonia, and mild increased pulmonary vascularity	Severe LV dysfunction with ejection fraction 20% (unchanged from baseline), moderate RV dysfunction (worse from baseline), moderate-to-severe PH with tricuspid regurgitation jet predicting $^3/_4$ systemic RV pressure, and moderate tricuspid and mitral valve regurgitation.	NT-pro-BNP 74160	0.21	10.1	MV PRVC mode, rate 40 bpm, TV 60 mL, PEEP 12 cmH_2O, PS +10 cmH_2O, PIP in the 30s cmH_2O, FiO_2 100%	Yes	None	Tocilizumab, remdesivir (incomplete)	35	N/A	Recovery, discharged home
Case 4	6 mo	LV non-compaction/ DCM with depressed biventricular function	Fever, increased work of breathing, decreased oral intake, diarrhea, cough, emesis, nasal congestion	Stable enlargement of the cardiothymic silhouette. Mild stable perihilar opacities.	Mildly dilated left ventricle with mildly depressed LV systolic function (EF 51%), mildly impaired LV diastolic function.	NT-proBNP 353	Not performed	Not performed	N/A	No	None	None	0	4	Recovery, discharged home. Readmitted 2 wk later for fever, diarrhea, fever. Discharged home.

(*Continued*)

Table. Continued

Case nos.	Age	Cardiac history	Presenting signs and symptoms	Key CXR findings	Key echocardiography findings	BNP, pg/mL	Troponin, ng/mL	Maximum CRP, mg/dL	Maximum respiratory support	Milrinone, yes/no	ECMO	COVID-19 treatment	Days in ICU	Days on ward	Outcome
Case 5	9 mo	ToF, right dominant CAVC, parachute left AV valve	Fever, increased work of breathing, hypoxemia, cough	Increased opacification with a new right pleural effusion	No echocardiogram acquired during admission	NT-pro-BNP 777	0.3	1.6	10 L HFNC FiO_2 50%	No	None	None	5	3	Recovery, discharged home. Readmitted 1 mo later with hypoxemia, discharged home. Death from unknown causes 2.5 mo after initial admission.
Case 6	18 y	HCM	Fever, increased work of breathing	Diffuse bilateral airspace opacities	LV hypertrophy with severe LV dysfunction	572	2.7	Not performed	MV VDR mode 50/18 cmH20, rate 20 bpm, FiO_2 100%, 40 PPM iNO	Yes	VV, VA ECMO	Hydroxychloroquine, azithromycin, tocilizumab, IVIG, convalescent plasma	31	N/A	Death due to recurrence of VT
Case 7	19 y	DILV with Fontan palliation followed by heart transplant 8 years ago	Poor oral intake, diarrhea, loss of taste, decreased appetite	No CXR acquired during admission	Normal echocardiogram after orthotopic heart transplant	NT-pro-BNP 1171	0.3	Not performed	None	No	None	None	0	9	Recovery, discharged home.

ALCAPA, anomalous left coronary artery from the pulmonary artery; *DCM*, dilated cardiomyopathy; *DILV*, double-inlet left ventricle; *EF*, ejection fraction; *FiO_2*, fraction of inspired oxygen; *HCM*, hypertrophic cardiomyopathy; *HFNC*, high-flow nasal cannula; *ICU*, intensive care unit; *iNO*, inhaled nitrous oxide; *IVIG*, intravenous immunoglobulin; *LV*, left ventricular; *MV*, mechanical ventilation; *N/A*, not available; *NT pro-BNP*, N-terminal-pro-hormone BNP; *PEEP*, peak end-expiratory pressure; *PH*, pulmonary hypertension; *PIP*, peak inspiratory pressure; *PPM*, parts per million; *PRVC*, pressure-regulated volume control; *PS*, pressure support; *RV*, right ventricular; *ToF*, tetralogy of Fallot; *TV*, tidal volume; *VA*, venoarterial; *VDR*, volumetric diffusive respirator; *VT*, ventricular tachycardia; *VV*, venovenous.

tachycardia to the 200s to improve diastolic filling. After a 10-day course of remdesivir, she was persistently SARS-CoV-2 positive by PCR and received 5 convalescent plasma infusions with subsequent negative SARS-CoV-2 PCR testing. Her hospital course was complicated by staphylococcal scalded skin syndrome, acute kidney injury (AKI) secondary to heart failure, and medical necrotizing enterocolitis. She was extubated on hospital day 33 to noninvasive positive pressure ventilation.

She remained an inpatient, on milrinone until surgical repair on hospital day 54. On hospital day 111 she was off respiratory support, with compensated heart failure on oral therapy.

Case 3

A 6-month-old male patient with a history of anomalous left coronary artery from the pulmonary artery surgically repaired at 2 months of age with moderate postoperative supravalvar aortic stenosis and severe left ventricular dysfunction with compensated heart failure maintained on enalapril, digoxin, carvedilol, furosemide, and aspirin presented with hypoxemia in the setting of 2 days of fever, decreased oral intake, and increased work of breathing. His CXR showed cardiomegaly, ground-glass opacity consistent with pneumonia, and increased pulmonary vascularity. Baseline echocardiogram had severe left ventricular dysfunction (left ventricular ejection fraction of 20%) and moderate supravalvar aortic stenosis (peak gradient of 35 mm Hg) in the region of the aortic transection from his LeCompte maneuver. Echocardiogram obtained during admission showed new pulmonary hypertension with right ventricular dysfunction, and left ventricular ejection fraction of 20% unchanged from patient's baseline. He had elevated N-terminal-pro-hormone BNP, troponin, and lactate concerning for worsening heart failure. He had markedly elevated inflammatory markers including ferritin, lactate dehydrogenase, CRP, procalcitonin, and interleukin-6. He was SARS-CoV-2 positive by PCR on admission. The patient had contact with 3 family members before admission, who had mild symptoms consistent with COVID-19 infection, and eventually tested positive for SARS-CoV-2 positive.

He required intubation and substantial ventilatory support due to acute respiratory distress syndrome. During intubation, he developed bradycardia and ventricular tachycardia requiring epinephrine and cardiopulmonary resuscitation. Epinephrine and milrinone infusions were started for decompensated heart failure. Inhaled nitric oxide was added for pulmonary hypertension with rapid improvement in oxygenation. He received tocilizumab and remdesivir. During hospital days 5-14, his inflammatory markers improved, and he weaned off epinephrine. Milrinone was continued until after extubation and initiation of enalapril. On hospital day 20 he was successfully extubated. He was discharged home on hospital day 35 on an enteral heart failure regimen, Lovenox (Sanofi-Aventis U.S., Bridgewater, New Jersey), and full oral feeds. At 58 days after discharge, he remained stable as an outpatient.

Case 4

An ex-36-week 6-month-old male patient with a history of left ventricular non-compaction and dilated cardiomyopathy with depressed biventricular function with compensated heart failure maintained on captopril, carvedilol, digoxin, aspirin, furosemide, and spironolactone presented with emesis and diarrhea in the setting of 1 day of fever, increased work of breathing, cough, nasal congestion, and decreased oral intake. He was SARS-CoV-2 positive by PCR on admission with no known sick contacts. Stool studies sent for rotavirus and norovirus were negative. Echocardiogram at baseline had mildly dilated left ventricle, mildly depressed left ventricular systolic function (left ventricular ejection fraction or 47 %), mildly impaired left ventricular diastolic function. Echocardiogram during admission was unchanged from baseline.

He required intravenous fluid resuscitation during admission. Home captopril and furosemide were held initially due to hypovolemia. He received empiric intravenous antibiotics for 48 hours. He was discharged home on hospital day 4 no longer on furosemide but otherwise on his home regimen.

He was readmitted 2 weeks later with fever, diarrhea, rash, and tachypnea requiring intravenous fluid resuscitation. His SARS-CoV-2 PCR remained positive. He was discharged home after 2 days; 81 days after his initial hospital discharge, he was stable as an outpatient.

Case 5

A 9-month-old-male patient with a history of trisomy 21, obstructive sleep apnea, hypothyroidism, tetralogy of Fallot, right dominant CAVC with parachute left AV valve, and pulmonary hypertension who had surgical repair at 3 months of age with placement of Melody valve (Medtronic, Minneapolis, Minnesota) in the left AV valve position and compensated heart failure on furosemide, sildenafil, and oxygen at night presented with intermittent cough, increased work of breathing, and hypoxemia in the setting of 2 days of fever.

His CXR was concerning for pulmonary edema and pneumonia (**Figure 2**; available at www.jpeds.com). He had an elevated CRP. N-terminal-pro-hormone BNP was elevated; however, it was improved from baseline. ST-segment changes were noted on telemetry, with reassuring electrocardiogram and serum troponin. He was positive for SARS-CoV-2 by PCR on admission with a known sick contact in his mother who had symptoms of COVID-19 infection before his admission. She did not receive SARS-CoV-2 testing.

After admission, he required escalation to 10 L of high-flow nasal cannula of respiratory support. He was started on empiric intravenous antibiotics for 48 hours and intravenous diuretics. Over the next week, he was able to wean on respiratory support and diuretics until he was on his home regimen. He was discharged home on hospital day 8.

He was readmitted 1 month after discharge for hypoxemia secondary to fluid overload. He improved with intravenous diuresis, and required a maximum of 2 L of nasal cannula. His SARS-CoV-2 PCR remained positive. He was discharged home on hospital day 6 on his home regimen. The patient died 2.5 months after his initial hospital discharge. His cause of death was thought to be related to his residual cardiac disease.

Case 6

An 18-year-old female patient with obesity and metabolic syndrome, type II diabetes, chronic hypertension, and a cardiac history of hypertrophic cardiomyopathy maintained on metoprolol presented with fever and respiratory distress. Her CXR had signs of diffuse bilateral airspace opacities. Echocardiogram at baseline demonstrated left ventricular hypertrophy. Echocardiogram on admission showed preserved biventricular systolic function, and left ventricular hypertrophy similar to baseline. She was positive for SARS-CoV-2 by PCR on admission with no known sick contacts.

She initially required intubation and mechanical ventilation for hypoxemic respiratory failure, then developed rapid decompensation with an oxygenation index of 51. She was transitioned to venovenous extracorporeal membrane oxygenation (ECMO) for refractory hypoxemic respiratory failure. She became hemodynamically unstable despite vasoactive medications, in the setting of ST-segment changes on electrocardiogram, and elevated serum troponin. She was escalated to venoarterial-ECMO for acute decompensated heart failure. Within 24 hours, she developed rapid ventricular tachycardia (**Figure 3**; available at www.jpeds.com) requiring defibrillation, and infusions of amiodarone and lidocaine. For COVID-19, she received hydroxychloroquine, azithromycin, tocilizumab, and convalescent plasma. For presumed myocarditis she received intravenous immunoglobulin and methylprednisolone. Over the next 2 weeks, she improved and was transitioned back to venovenous-ECMO on ICU day 17, with decannulation 4 days later.

She remained on mechanical ventilation, vasoactive support, anti-arrhythmic agents, and on renal-replacement therapy for AKI until she had recurrence of ventricular tachycardia and died on hospital day 31.

Case 7

A 19-year-old female with obesity and type II diabetes mellitus, stage II chronic kidney disease, mild intermittent asthma, and a cardiac history of double inlet left ventricle with Fontan palliation followed by cardiac transplant 8 years ago presented with 5 days of diarrhea, decreased appetite with poor oral intake for 4 days, and loss of taste for 3 days. She was maintained on atorvastatin, lisinopril, CellCept (Genentech USA, Inc, South San Francisco, California), and tacrolimus before her presentation.

Creatinine was elevated concerning for AKI. N-terminal-pro-hormone BNP was elevated. She was positive for SARS-CoV-2 by PCR on admission. Baseline echocardiogram showed normal biventricular function after orthotopic heart transplant, with borderline dilated right ventricle. Echocardiogram during admission was unchanged. An electrocardiogram showed new first-degree AV-block with a prolonged PR-interval from her baseline of 180 milliseconds to 214 milliseconds. BK virus urine and serum tests were negative. Stool studies were negative.

She required intravenous fluid resuscitation for hypovolemia. Her mycophenolate mofetil was halved while she was actively infected with COVID-19; she remained on tacrolimus. Her creatinine improved; however, it did not return to baseline. She was discharged on hospital day 9 on her home regimen with the exception of lisinopril, which was held due to her AKI. At 72 days after hospital discharge, she was stable as an outpatient.

Discussion

In this series of hospitalized patients with pre-existing cardiac conditions, we observed that new or worsening heart failure was common. Each of these cases is believed to represent acute COVID-19 infection and not multisystem inflammatory syndrome in children.[2] Four of the 7 patients presented with acute congestive heart failure: 1 with de novo acute heart failure (case 6), and 3 with acutely decompensated chronic heart failure (case 2, case 3, case 5). In 1 case (case 2), the decompensated heart failure was initially believed to be progression of the child's underlying disease, thus delaying diagnosis. The cases with the most severely decompensated cardiac function demonstrated cardiogenic shock requiring inotropes (case 2, case 3, case 6), and in 1 case with venoarterial ECMO (case 6).

In addition to heart failure, new cardiac arrhythmias and evidence of myocardial inflammation were noted. Four of the seven patients developed cardiac arrhythmias or new electrocardiogram abnormalities with no previous history of arrhythmias (case 2, case 3, case 6, case 7). Three of these also had the longest clinical courses (case 2, case 3, case 6). Two also had evidence of acute myocardial inflammation vs acute myocardial injury with elevated troponins (case 3, case 6), 1 of whom had accompanying ST-segment changes on electrocardiogram concerning for acute coronary syndrome vs myocarditis with arrhythmia eventually leading to death (case 6).

Consistent with previous reports of severe acute COVID-19 in children, the majority of our cases were younger than 1 year of age.[3,4] Three of the 5 patients had CAVC defect and trisomy 21 (case 1, case 2, case 5).

Currently, there are no pharmacotherapies for COVID-19 or its associated cardiovascular disease that have high-quality data supporting clinical efficacy. Although awaiting the results of several clinical trials currently underway, intravenous immunoglobulin, convalescent plasma, hydroxyurea, remdesivir, and tocilizumab are currently being used in a case-by-case basis in both adults and children. Three of our patients received 2 or more of these therapies with varying results.

COVID-19 was community acquired for all 7 of our patients. ■

Submitted for publication Jul 7, 2020; last revision received Jul 23, 2020; accepted Jul 23, 2020.

Reprint requests: Matthew E. Oster, MD, MPH, Sibley Heart Center Cardiology, Children's Healthcare of Atlanta, 2835 Brandywine Rd, Suite 300, Atlanta, GA 30341. E-mail: osterm@kidsheart.com

References

1. Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. Circulation 2020;141:1903-14.
2. Center for Disease Control and Prevention Health Alert Network. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19) [Internet]. United States: CDCHAN; 2020 May 14 [cited 2020 Jul 1]. https://emergency.cdc.gov/han/2020/han00432.asp. Accessed July 1, 2020.
3. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr 2020. in press.
4. Center for Disease Control and Prevention Morbidity and Mortality Weekly Report. Coronavirus Disease 2019 in Children - United States, February 12–April 2, 2020 [Internet]. United States: CDCMMWR; 2020 Apr 10 [cited 2020 Jul 1]. https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm?s_cid=mm6914e4_w. Accessed July 1, 2020.

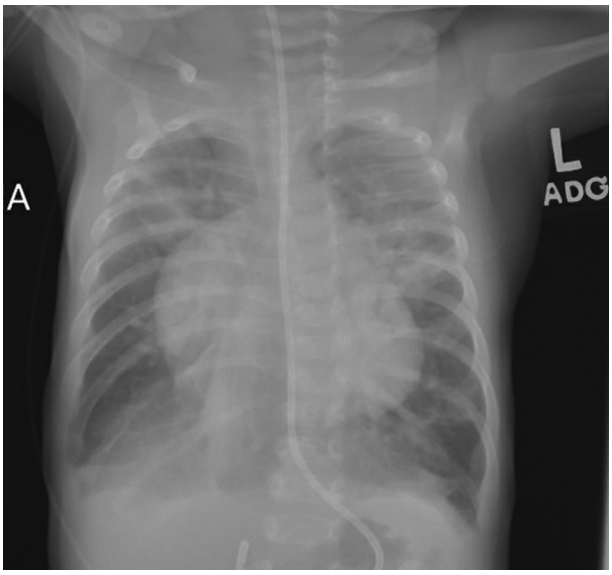

Figure 1. Chest radiograph of a 3-month-old female patient with trisomy 21 and unrepaired CAVC obtained on admission with cardiomegaly, shunt vascularity, lung hyperinflation, and new linear areas of airspace opacity representing atelectasis vs underlying superimposed pneumonia.

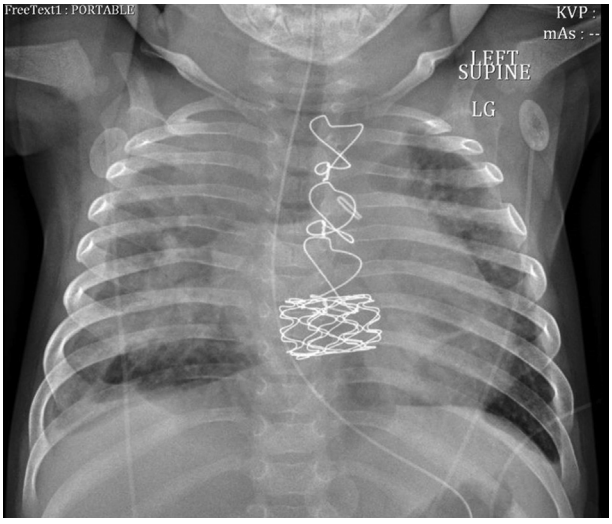

Figure 2. Chest radiograph of a 9 month-old-male patient with a history of trisomy 21, obstructive sleep apnea, tetralogy of Fallot, pulmonary vascular hypertension, and right dominant atrioventricular canal with parachute left AV valve who had surgical repair at 3 months of age with the placement of Melody valve in the left AV valve position obtained on hospital day 2 at time of transfer to the cardiac intensive care unit with increased airspace opacification in the right upper lobe along with increased right pleural effusion apically and laterally. Persistent perihilar and lower lobe opacities are also noted.

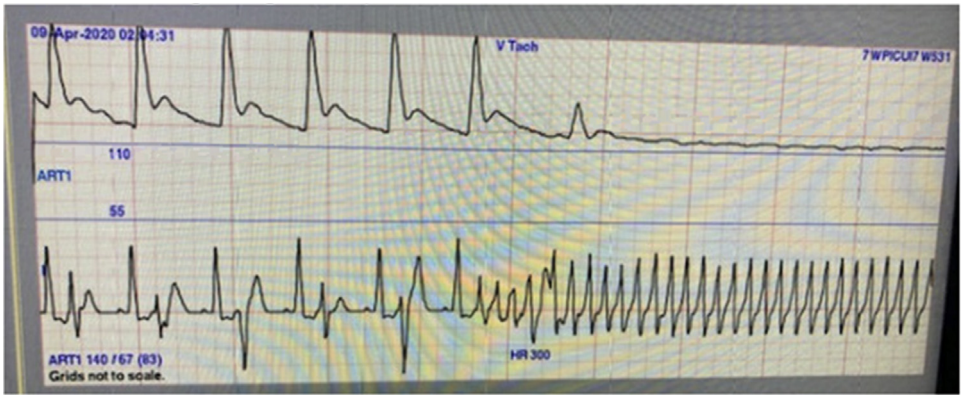

Figure 3. Rhythm strip of an 18-year-old female patient with hypertrophic cardiomyopathy obtained during admission with ventricular bigeminy transitioning into monomorphic ventricular tachycardia at 300 beats per minute with significant effect on arterial line tracing.