Severe Sinus Bradycardia: An Unusual Cardiac Manifestation of COVID-19

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Abstract
There has been an accumulating evidence of association between COVID-19 (coronavirus disease 2019) infection and cardiovascular complications. We describe a case of a 58-year-old lady with a history of systolic heart failure and COVID-19 infection, who developed persistent symptomatic bradycardia, requiring pacemaker placement as unusual conductive tissue involvement of this novel coronavirus.

Keywords
bradycardia, Micra pacemaker, COVID-19

Learning Objectives
• To anticipate and diagnose severe sinus bradycardia associated with the novel coronavirus.
• To understand the potential mechanisms responsible for severe sinus bradycardia associated with COVID-19 without evidence of overt myocarditis.

History of Presentation
A 58-year-old female with a past medical history of hypertension, hyperlipidemia, diabetes, and heart failure with reduced ejection fraction (EF; 45% to 50%) secondary to viral myocarditis 20 years ago. She presented to the emergency room with a 1-week history of fatigue, cough, dyspnea, vomiting, and diarrhea. At the initial evaluation, the blood pressure was 82/69 mmHg, and the heart rate was 109 beats per minute. The respiratory rate was 18 breaths per minute, and the oxygen saturation was 96% on room air. The temperature was 37.2 °C. Vitals were consistent with sinus tachycardia and hypotension, which were corrected with intravenous fluid resuscitation. Physical examination demonstrated signs of dehydration, dry mucous membranes, in addition to a weak rapid pulse. There was no evidence of central venous distention or peripheral edema. Lungs were clear, and there were no signs of hypoxemia or respiratory distress.

Past Medical History
Our patient had experienced viral myocarditis following an acute viral illness at the age of 32 years. At that time, an echocardiogram showed a severely decreased left ventricular (LV) systolic function (LVEF 10% to 15%) and a dilated LV cavity with normal wall thickness. Subsequent coronary catheterization around the time of diagnosis and 1 year ago showed normal coronaries. She did not require hospitalization or develop heart failure exacerbation in the past 15 years. The most recent echocardiogram showed improved LVEF to 45% to 50%. Her home medications were metoprolol succinate, lisinopril, amlopidine, atorvastatin, and aspirin.
brain natriuretic peptide were normal. Chest X-ray showed increased pulmonary vascular markings without evidence of infiltration. The initial electrocardiogram showed normal sinus rhythm with a ventricular rate of 98 beats per minute, QTc interval was normal (436 ms; Figure 1). Real-time polymerase chain reaction confirmed COVID-19 positive status. The patient had a positive test with a low cycle threshold, indicating a high viral load. C-reactive protein was slightly elevated at 37 mg/L. Other inflammatory markers, including D-dimer, ferritin, and lactate dehydrogenase, were normal.

Hospital Course

The patient’s acute kidney injury improved; her pulmonary status progressively declined. On day 3 of hospitalization, the patient required oxygen therapy (nasal cannula 2 L/min) to maintain oxygen saturation >94%, chest X-ray demonstrated evolving bilateral pulmonary infiltrates. Therefore, she was started on dexamethasone therapy 6 mg daily. During days 3 to 5 of hospitalization, the patient developed worsening hypoxemia and increasing oxygen requirement to 4 L/min. She was started on remdesivir 200 mg daily on hospital day 5. Concurrently, the patient began to experience new-onset, asymptomatic sinus bradycardia (heart rate 35-45 beats/minute range; Figure 2). Electrocardiogram on day 5 showed sinus bradycardia with occasional premature ventricular complexes and low voltage seen in precordial leads V3 through V6. Dexamethasone was considered a possible culprit, given the temporality with the onset of bradycardia. Steroid course was switched to prednisone 40 mg daily; then the dose was cut in half and stopped without a significant heart rate change. Thyroid function and repeat troponin were normal. An echocardiogram obtained on day 6 showed mildly decreased LV function (LVEF 45% to 50%).

On days 7 to 9 of the hospital stay, the patient had blunted chronotropic responses. She has concurrently experienced symptoms of lightheadedness and dizziness on ambulation. On day 10, heart rate reached a nadir of 21 beats per minute with a blood pressure of 80/50 mmHg, requiring atropine administration and temporary venous pacing. Subsequently, the patient received a Micra pacemaker for persistent bradycardia.1

Discussion

Against the stark backdrop of the global pandemic, the scientific and medical communities’ understanding of COVID-19-related arrhythmias continue to evolve among patients who are critically ill with COVID-19.2,3

The potential underlying mechanisms include hypoxia, autonomic dysregulation, myocarditis, exaggerated immune response (eg, cytokine storm), myocardial stretch, myocardial ischemia, electrolyte imbalances, intravascular volume...
depletion, and drug-induced side effects. Unfortunately, there is a paucity of research on bradyarrhythmias among COVID-19 patients (compared with tachyarrhythmias), and bradyarrhythmia indicates a poor prognosis, even without coexistent acute cardiac injury.

Although cytokines are known to trigger arrhythmia by modulating the expression and function of ion channels, our patient had a mild elevation of C-reactive protein and normal inflammatory markers, including D-dimer, ferritin, and lactate dehydrogenase. Hence, a cytokine storm and inflammatory channelopathies were unlikely to explain why she experienced a severe symptomatic sinus bradycardia. Another possibility was acute myocarditis, with a subsequent electrical imbalance and gap junction dysfunction. In more detail, the intracellular presence of the virus results in cytotoxicity and indirect damage through the migration of infected alveolar macrophages to the myocardium and cell-mediated cytotoxicity, whereby primed CD8+ T lymphocytes cause inflammation. Yet, when an echocardiogram and troponin level were repeated during her episodes of bradycardia, it revealed pre-COVID-19 infection EF and normal levels of troponin, which makes significant myocarditis and acute cardiac injury unlikely.

Of course, pulmonary hypertension, severe acute respiratory distress syndrome, and heart failure that strain the right ventricle can each predispose a patient to an increased risk of arrhythmias. However, our echocardiogram did not reveal a significant dilation in her chamber. Other causes, like myocardial ischemia and electrolyte imbalance, were excluded, given the lack of new regional wall motion abnormality, normal troponin levels, brain natriuretic peptide, and normal electrolytes. While we considered drug interaction, there was no significant chronotropic recovery when the patient stopped taking her steroid therapy and remdesivir.

Ultimately, we are left to speculate over the cause of our patient’s bradyarrhythmia. It may be due to direct viral infiltration of the sinoatrial (SA) nodal cells or acute lung injury that led to hypoxia. The latter can activate anaerobic glycolysis, thereby reducing intracellular pH, spurring gap junction dysfunction, and reduced electrical coupling. It is also worth noting that the COVID-19 virus uses the spike protein to bind the angiotensin-converting enzyme 2 (ACE2) receptors on the cell membrane, and ACE2 expression has been demonstrated in the SA nodal cells. It can explain the increased susceptibility of the SA nodal cells to the viral injury. Researchers have also noted conduction disturbances with ACE2 receptor overexpression in experimental animal models.

Importantly, our patient also has a history of viral myocarditis and systolic heart failure on guideline-directed medical therapy. Therefore, her remote cardiac injury with remodeling can also increase her susceptibility to COVID-19-mediated cardiac injury. When infected with COVID-19, she could have bradyarrhythmias from direct SA nodal cells.

Figure 2. Shows severe sinus bradycardia.
damage or become unstable from an increased metabolic demand and reduced cardiac reserve. This imbalance could have triggered cardiac bradyarrhythmias or aggravated (if not unmasked) preexisting damage to her conduction tissue.

**Conclusion**

After contracting an acute infection of COVID-19, our patient experienced severe, persistent sinus bradycardia that required a permanent pacemaker in order to alleviate her symptoms. As discussed, there are several potential mechanisms that increase the risk of bradyarrhythmias during a COVID-19 infection, including various modes of myocardial and conductive cells injury, as well as extracardiac processes that can trigger de-novo bradyarrhythmias (or unmask a preexisting conductive tissue disease). Given the protracted timeline of the COVID-19 pandemic, further research is required to provide clinicians with a better understanding of arrhythmia pathophysiology, patient prognosis, and to validate management protocols in order to improve patient outcomes, increase health system capacity, and protect scarce resources.

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**Ethics Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

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