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Case Report

Hypoxic bradycardia: an enigma in coronavirus disease 2019

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ABSTRACT

Coronavirus disease 2019 varies from asymptomatic to severe acute respiratory syndrome with multiple organ involvement, primarily involving the microvasculature and heart. Acute myocardial injury is the most frequently observed and reported cardiac complication with acute coronary events, acute left ventricular systolic dysfunction, and cardiac arrhythmias, but sinus bradycardia reported only in a few cases. The development of sinus bradycardia can be crucial warning sign of onset of severe cytokine storm. The primary determinant of severity of COVID-19 is aging and co-morbidities such as diabetes and hyperlipidemia with dysregulated immunological status. Patients with pre-existing cardiovascular disease infected with COVID-19 have increased risk of severity and mortality. Literature available regarding the occurrence of bradycardia is limited, and electrophysiology studies in COVID-19 patients have shown sinus bradycardia, heart block, bundle branch block, and intraventricular conduction delay. The pathophysiological mechanism regarding the occurrence of bradycardia is not yet known entirely. Cardiac manifestations could be attributed to multiple clinical etiologies, including direct viral myocardial damage, inflammatory response, hypoxia, hypotension, downregulation of angiotensin-converting enzyme 2 (ACE-2), drug toxicity, and endogenous toxicity of catecholamine adrenergic status, also severe hypoxic damage of lungs by COVID-19 can also act as a trigger. We report one such case of bradycardia due to COVID-19 detected through intensive monitoring and managed successfully in the ICU of tertiary care dedicated COVID-19 hospital. Bradycardia in COVID-19 is a rare clinical phenomenon, could be a worst prognostic marker. If detected early may help in prognostication and, if managed appropriately, will avert a life-threatening complication.

Keywords: Bradycardia, COVID-19, Cytokine storm, Cardiovascular

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a contagious viral illness caused by a strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can be transmitted even when the host is asymptomatic, thus resulting in widespread COVID-19 pandemic. It has numerous presentations, from asymptomatic to severe acute respiratory syndrome with multiple organ involvement, primarily the microvasculature and heart. Various studies have shown a link between age, cardiovascular disease, and COVID-19. The pre-existing cardiac disease could be an attributing factor in mortality in COVID-19.[1]

Acute myocardial injury is the most frequently observed and reported cardiac complication in 8-12% of all COVID-19 patients.[2] The clinical feature reported includes unstable angina, thromboembolic events, acute decompensated heart failure, and cardiac arrhythmias, mainly tachyarrhythmias.[2,3] Another cardiac manifestation of COVID-19 is bradycardia, the literature available pertaining to the occurrence of bradycardia is limited. A

global survey of electrophysiologists revealed that of 663 respondents, 51 (8%) reported significant sinus bradycardia, 51 (8%) reported complete heart block, 39 (5.9%) reported first- or second-degree Atria-ventricular block and 26 (3.9%) reported bundle branch block or intraventricular conduction delay in COVID-19 patients.[4]

For cardiovascular disease (CVD), age is the most significant risk factor, and the sequelae of aging on immune function may be equally crucial for COVID-19 vulnerability and severity. Numerous other risk factors, such as diabetes and hyperlipidemia, affect immune function. It may result in dysregulated immunologic status, which corresponds to an elevated risk of CVD.[5] Further, patients may present with symptoms during the disease or later after acute symptoms of infection have subsided. Thus, clinicians must be able to identify this clinical entity and manage the symptoms promptly. We report one case of bradycardia due to COVID-19, which was detected through intensive monitoring and managed successfully in ICU in dedicated tertiary care COVID hospital.

CASE REPORT

A 65-year-old male patient presented with chief complaints of intermittent fever, sore throat, dry cough for five days, and shortness of breath for one day and tested positive for reverse transcriptase polymerase chain reaction (RT-PCR) COVID-19. The patient had not been vaccinated for the same. He had been a known type 2 diabetic for the past four months and was on the tablet metformin 500 mg bd, with no other known comorbidities. His vital parameters at the time of presentation were: pulse rate (PR) of 80-90/min, blood pressure (BP) of 130/80 mmHg, and 16-18 breaths/min respiratory rate. The patient maintained an oxygen saturation of 88% in room air and an oxygen saturation of 96% on O_2 given by a high FiO_2 partial rebreathing face mask. On auscultation, crepitations were heard in bilateral lower lung fields and normal heart sounds. The arterial blood gas analysis showed PaO_2/FiO_2 ratio <300. A 12-lead electrocardiography (ECG) showed normal sinus rhythm, and a chest X-ray revealed bilateral lower zone infiltrates and no cardiomegaly (Figure 1). The patient was admitted under the severe category of COVID-19-SARS in the intensive care unit. Injection of meropenem 1 g iv TDS, tab dexamethasone 6 mg od, tablet pantoprazole 40 mg bd, tablet vitamin C 500 mg od, multivitamin tablets, and self-proning was started. Over the next two days, his general condition deteriorated, PaO_2/FiO_2 <200, and non-invasive ventilation had to be started (with pressure support:14 cmH_2O, PEEP: 8 cmH_2O, FiO_2: 0.8%). On day eight of the illness, the patient was noted to have bradycardia but no associated symptoms. The heart rate was between 40-46 bpm, and simultaneous blood pressure readings were 117-122/60-70 mmHg, but no complaints of tiredness, chest discomfort, palpitation, sweating, or signs of heart failure. The patient was given an injection of atropine 0.6mg intravenously once when his heart rate was around 40 beats per minute, cardiac enzymes were done CK-NAC=95 U/I and CK-MB=26 IU/l, and 12-lead ECG showed sinus bradycardia with a heart rate of 50 beats/minute. A provisional diagnosis of COVID-19 pneumonitis with diabetes mellitus and asymptomatic bradycardia for evaluation was made. The bedside echocardiography facility was unavailable, as the patient was on non-invasive ventilation, so it was not safe to shift the patient for the same, so a 2D-echo could not be done. The pro-BNP level was within normal limits. Inflammatory markers were elevated, and D-dimer was greater than 1000 ng/dl; hence therapeutic dose of anticoagulation was started. Inflammatory markers and D-dimer were monitored at regular intervals. The physicians advised to start him on oral atorvastatin once daily and aspirin 75 mg once daily. Episodes of bradycardia continued from the 8th day of admission till the 14th day. During the ICU stay, the patient had episodes of fever, low-grade intermittent, not associated with shivering. During episodes of bradycardia, his temperature ranged from 98 degrees to 100 degrees Fahrenheit. His condition progressively improved, and he was gradually de-escalated from non-invasive mechanical ventilation to a high FiO_2 partial rebreathing face mask and then later to a simple face mask. Subsequently, he maintained acceptable oxygen saturation in room air after 22 days from admission and was transferred to the ward on the 26th day. His ECG recordings done in the later stages showed normal sinus rhythm. Later he was tested for RT-PCR COVID-19 negative and was discharged after 32 days of hospitalisation.

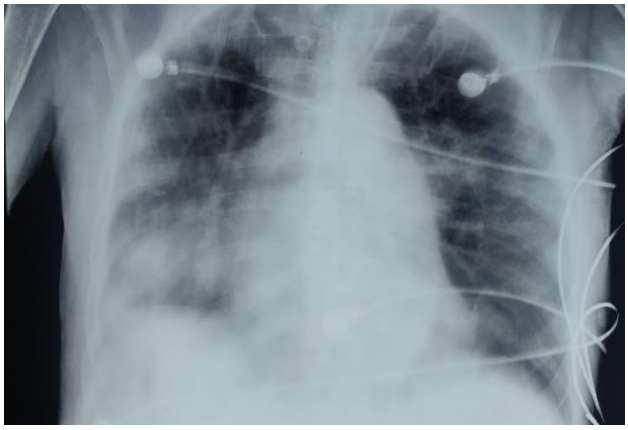

Figure 1: Chest X-ray showing bilateral lower zone infiltrates.

DISCUSSION

The mechanism of cardiovascular injury following COVID-19 infection can be multifactorial, including direct viral myocardial damage, inflammatory response, hypoxia, hypotension, and interaction with angiotensin converting enzyme-2 (ACE-2) and its downregulation, specific drug toxicities, and intrinsic catecholamine excess status.[6] Acute myocardial injury is a common phenomenon in COVID-19 patients and is associated with the worst prognosis. An analysis of 150 patients with COVID-19 showed that of 68 mortalities, 7% had myocardial damage,

and 22% had myocardial damage and respiratory failure.[7] COVID-19 patients with myocardial injury have the potential for developing cardiac arrhythmias, but the development of sinus bradycardia has been seen only in a few cases. Also, severe hypoxic damage to the lungs by COVID-19 could trigger atrial arrhythmias. The contribution of COVID-19 to the development of cardiac arrhythmia remains unclear.

The pathophysiology of relative bradycardia is not so far fully understood. A few proposed mechanisms regarding the pathogenesis of bradycardia include the release of inflammatory cytokines, especially interleukin-6, increased vagal tone, and direct pathogenic effects on the heart.[8] Ye et al hypothesized that the immediate inhibitory effect of SARS-COV-2 on the sinoatrial node might be the primary mechanism of relative bradycardia.[8] They further proposed that cardiac pacemaker cells can act as a target for inflammatory cytokines. It can change heart rate dynamics or sensitivity to neurotransmitters during systemic irritation resulting in inflammation.[9] Recent studies showed correlation of COVID-19 severity to the development of cytokine storm.[10] Thus the development of bradycardia may present at a particular stage of the illness, thus alarming the physician for prompt management and further evaluation in these patients.

A case series of six patients of Asian origin showed that all patients with bradycardia had increased D dimer levels and were symptomatic with light-headedness, fatigue, and near syncope. Still, none showed any structural abnormality on echocardiography.[11] They proposed that proinflammatory indicators such as IL-6 and D-dimer levels, markers of systemic inflammation, may contribute to cardiac manifestations of COVID-19.[9]

The development of bradycardia usually ranges from four to 15 days of hospitalisation, which concurs simultaneously when a cytokine storm occurs. Although the data available is limited, it is shown that mortality was associated with the rise of cardiac troponin I on day 16 of illness. However, more research is needed to prove this correlation.[12] Therefore, estimating proinflammatory and anti-inflammatory cytokines, monitoring heart rate variability (HRV), and assessing underlying comorbidities are necessary during the episode of relative bradycardia. In this case, we measured inflammatory markers, which were markedly elevated. The timing and the level of raised inflammatory markers strongly correlate with cytokine storm.[13] When our patient was thoroughly monitored, his cardiac enzymes were marginally elevated, he was given vagolytic in the form of atropine, and dopamine infusion was kept on standby. However, it was not required in this patient.

Studies have shown an association between azithromycin and hydroxychloroquine use leading to bradyarrhythmias and QTc prolongation. But our patient did not receive this drug combination.[14] This drug should be stopped immediately if the patient is on any medication that causes bradycardia. Bradycardia could be a prognostic marker pointing to the worst outcome.[15]

Echocardiography could have been a relevant investigation, although literature shows that there may be no structural abnormality even in symptomatic bradycardia due to COVID-19. Relative bradycardia outlines the mechanism of dissociation between pulse and temperature.[9] This mechanism has been turned up in many infectious diseases.[16] There is no such correlation in the literature for patients with COVID-19. Also, bradycardia was observed at 100 degrees Fahrenheit, whereas in the above conditions, the patients manifested bradycardia at higher temperatures. Therefore, further studies are needed to know the exact mechanism of bradycardia in COVID-19 patients.

The individuals with pre-existing serious cardiac conditions showed consistent evidence of COVID-19 susceptibility and severity. Contradicting the above finding, a retrospective study from the United Kingdom found little difference between pre-existing cardiac disease in COVID-19 (11.4%) and non-COVID-19 (12%) deaths.[17] The pathophysiology and outcome of SARS-CoV-2 in patients with comorbidities is still a matter of research. Studies have shown that the inflammatory mediators produced following host cell lysis during rapid viral replication cause the worst outcome. Many studies demonstrate that proinflammatory cytokines probably activate the T–helper-1 cell response. The accelerated release of inflammatory cytokines results in elevated levels of serum inflammatory markers. This inflammatory response can result in thrombosis also. Studies demonstrate the downregulation of ACE-2 receptors by SARS-COV-2 infection, resulting in an elevated level of angiotensin-2, which can result in severe systemic inflammation, oxidative organ damage, and acute respiratory distress syndrome. All these events result in a severe cytokine storm[18] which may correlate with disease severity and outcome.

CONCLUSION

Bradycardia in COVID-19 is a rare clinical phenomenon, and it could be a prognostic marker pointing to worse. If detected early, it may help in prognostication and, if managed appropriately, will avert a life-threatening complication. More importantly, extensive studies should be conducted in populations that developed bradycardia in COVID-19 to predict disclose the same disease course and severity.

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