

Bradycardia in a Patient with Severe COVID-19

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Heart rate disorders and in particular sinus arrhythmias are known to accompany viral infections. Sinus tachycardia is prevalent in the presence of increased body temperature and respiratory rate. However, bradycardia has also been described for centuries to complicate viral illnesses. As of March 2022, people are still contracting coronavirus disease 2019 (COVID-19), yet sinus bradycardia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is not well documented. We present a male patient diagnosed with severe COVID-19 infection presented to our department with severe bradycardia. In addition, we conducted a review of medical literature addressing similar associations and present it together with our case.

PATIENT DESCRIPTION

A 47-year-old Israeli Jewish male of Yemeni-Kurdish origin presented to our department with severe COVID-19 infection. The patient was diagnosed with SARS-CoV-2 infection 11 days prior to his admission, while he became symptomatic one day earlier (12 days before admission). His complaints included weakness, headache, and fever up to 40°C. The patient had no significant medical history of taking medications on a usual

basis. G6PD-deficiency was known since birth. He had no history of smoking and denied alcohol abuse or illicit drugs use. His baseline heart rate was 45 beats per minute. He participated in intensive sports activities in the last year, including long bike riding and tennis playing. No cardiac history was known. The patient lived in Nigeria for the last 16 years and was initially admitted to a hospital in Nigeria because of dyspnea. His oxygen saturation was 88% on room air and 96% with nasal cannula (10 L/min). His heart rate during hospitalization was 40–45 beats per minute (bpm). During his hospital stay in Nigeria he was treated with intravenous (IV) meropenem (1 grams 3 times a day), IV dexamethasone (4 mg twice a day), and subcutaneous (SC) enoxaparin (40 mg per day). A computed tomography (CT) scan of his lungs demonstrated multifocal bilateral pulmonary infiltrates suspicious of atypical pneumonia due to COVID-19 infection [Figure 1A]. Blood tests from his stay demonstrated white blood cell count (WBC) 3.37 K/µl, lymphocyte count 1.16 K/µl, C-reactive protein (CRP) 8 mg/dl. After 4 days of hospitalization in Nigeria the patient decided to fly to Israel, the flight lasted 5.5 hours. He denied any aggravation or new complaints during the flight. Blood oxygen saturation was stable above 94% with nasal-cannula oxygen supplementation, and his heart rate was 35–40 bpm on average. No drugs or sedatives were given during the flight.

On arrival, his heart rate was measured 29 bpm, no fever, oxygen saturation 92% on room air, 95% with nasal-cannula (5 L/min). He reported no chest pain

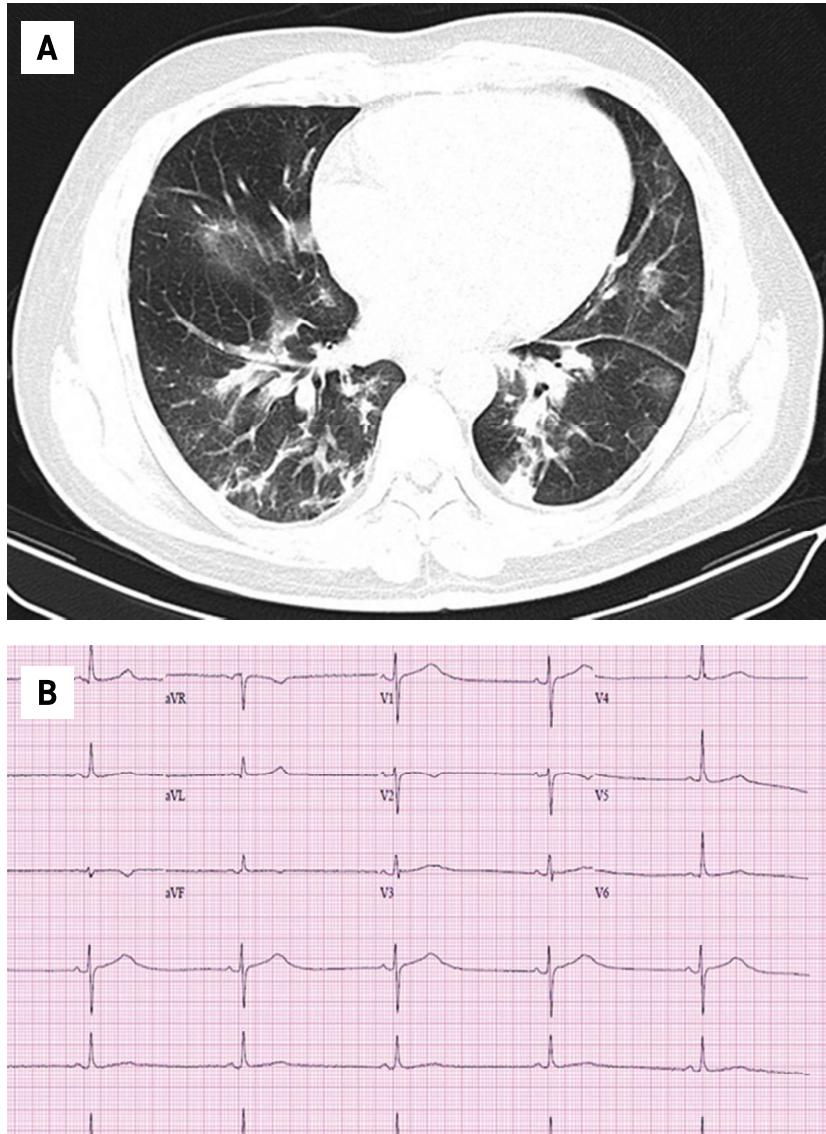
or palpitations and no other complaints. Physical examination was of no significant findings. Chest-X ray showed bilateral infiltrates. Laboratory tests showed WBC 6.16 K/µl, lymphocyte count 0.8 K/µl, hemoglobin 10.7 g/dl, CRP 53 mg/dl, procalcitonin 6.29 ng/ml, D-Dimer 953 ng/ml, and slightly elevated liver enzymes and cholestatic parameters, negative troponin, normal thyroid function, and normal electrolytes. Three consecutive electrocardiograms conducted on admission to the emergency department as well as in our department showed sinus bradycardia with ventricular rate of 29–34 bpm [Figure 1B]. A polymerase chain reaction (PCR) test on the day of admission was positive with E-gene of 27.6, and N-gene 29.6. Serological test showed CoV-2-IgG titer of 22.6 S/CO. Blood cultures drawn on admission were negative. The patient was given remdesivir, dexamethasone, and enoxaparin. The whole clinical picture was suggestive of severe COVID-19 infection accompanied with sinus bradycardia. Later, the patient recovered and his heart rate returned to baseline.

COMMENT

Sinus bradycardia is defined as heart rate lower than 60 heart bpm. The etiology of this disorder includes intrinsic and extrinsic factors. For centuries, infectious diseases have been thought to cause bradycardia. Referred to as relative bradycardia in some textbooks and studies, relative bradycardia is defined as a mismatch between body temperature

Figure 1. Heart and lung scans

- [A] Computed tomography scan of the lungs (8th day of disease)
 [B] Electrocardiogram on admission (12th day of disease)



and heart rate in which an increase of body temperature causes no appropriate increase in heart rate as expected. This phenomenon was reviewed by Cunha [1] who illustrated different causes of relative bradycardia with an emphasis on infectious agents. Yellow fever, dengue fever, and viral hemorrhagic fever were more common. With reference to the coronaviridae family, bradycardia was described during the outbreak of severe

acute respiratory syndrome (SARS) virus in 2003 as Yu et al. [2] showed that 18 (14.9%) out of 121 patients diagnosed with SARS infection developed a new onset but transient sinus bradycardia. The authors showed that bradycardia was related to disease course and found to be more prevalent during the first 2 weeks of illness. Unlike tachycardia, bradycardia was transient and lasted for an average of 2.6 days. The mean heart rate during bra-

dycardia was 43 bpm, range 38–49 bpm. None of the patients had experienced bradycardia during the follow-up period and no intervention was needed.

Unsurprisingly, SARS-CoV-2 infection was also shown to be associated with bradycardia as seen with other corona viruses. In a global survey answered by physicians treating patients with COVID-19 [3] 51 of 663 respondents (7.6%) reported that sinus bradycardia and complete heart block were the most common bradyarrhythmias seen in their practice. However, Capoferri and colleagues [4], in a study including 110 patients diagnosed with COVID-19, found that the prevalence of bradycardia was much higher than 40 (56%) out of 71 patients who had fever during their hospital stay experienced relative bradycardia. Patients with bradycardia in the study were older and had higher temperatures. This phenomenon appeared after a median time of 9 days and was not associated with unfavorable outcomes.

With regard to possible causes of decrease heart rate in patients with COVID-19, various mechanisms were proposed, including hypoxemia, direct pathogen effect on sinoatrial (SA) node, and secondary reaction to drugs used for the treatment of COVID-19 such as hydroxychloroquine and remdesivir. The higher rate of angiotensin converting enzyme II (ACE2) receptors in non-respiratory organs, including the cardiovascular system, as demonstrated by Zou et al. [5] using single-cell RNA sequencing (scRNA-seq) has been widely recognized as an explanation for cardiac involvement in COVID-19.

CONCLUSIONS

Sinus bradycardia is common in patients with COVID-19, particularly those with severe disease, and tends to appear late in the clinical course. This phenomenon is likely transient and necessitates no intervention. However, physicians treating COVID-19 patients should pay attention to this disorder and consider monitoring, especially in older patients treated with

beta-blockers or those vulnerable to a decrease in heart rate.

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Capsule

Memory B cell repertoire from triple vaccinees against diverse SARS-CoV-2 variants

Wang et al. examined whether sera from individuals who received two or three doses of inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine could neutralize authentic Omicron. The seroconversion rates of neutralizing antibodies were 3.3% (2 out of 60) and 95% (57 out of 60) for individuals who had received 2 and 3 doses of vaccine, respectively. For recipients of three vaccine doses, the geometric mean neutralization antibody titer for Omicron was 16.5-fold lower than for the ancestral virus (254). The authors isolated 323 human monoclonal antibodies derived from memory B cells in triple vaccinees, half of which recognized the receptor-binding domain and showed that a subset (24 out of 163) potently neutralized all SARS-CoV-2 variants of concern, including Omicron. Therapeutic treatments with representative broadly

neutralizing monoclonal antibodies were highly protective against infection of mice with SARS-CoV-2 Beta (B.1.351) and Omicron. Atomic structures of the Omicron spike protein in complex with three classes of antibodies that were active against all five variants of concern defined the binding and neutralizing determinants and revealed a key antibody escape site, G446S, that confers greater resistance to a class of antibodies that bind on the right shoulder of the receptor-binding domain by altering local conformation at the binding interface. These results rationalize the use of three-dose immunization regimens and suggest that the fundamental epitopes revealed by these broadly ultrapotent antibodies are rational targets for a universal sarbecovirus vaccine.

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Eitan Israeli

Capsule

Three exposures to the spike protein of SARS-CoV-2 by either infection or vaccination elicit superior neutralizing immunity to all variants of concern

Antibody-mediated protection is challenged by the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VoCs) with immune escape properties, such as omicron (B.1.1.529), which is rapidly spreading worldwide. Wratil and co-authors reported neutralizing antibody dynamics in a longitudinal cohort of coronavirus disease 2019 convalescent and infection-naïve individuals vaccinated with mRNA BNT162b2 by quantifying SARS-CoV-2 spike protein antibodies and determining their avidity and neutralization capacity in serum. Using live-virus neutralization assays, the authors showed that a superior infection-neutralizing capacity against all VoCs,

including Omicron, developed after either two vaccinations in convalescents or a third vaccination or breakthrough infection of twice-vaccinated, naïve individuals. These three consecutive spike antigen exposures resulted in an increasing neutralization capacity per anti-spike antibody unit and were paralleled by stepwise increases in antibody avidity. They concluded that an infection-plus-vaccination-induced hybrid immunity or a triple immunization can induce high-quality antibodies with superior neutralization capacity against VoCs, including Omicron.

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