



Symptomatic Bradycardia in Covid-19 Hospitalized Patients: A Case Series

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ARTICLE INFO

Article history:

Received 8 June 2021

Revised 25 July 2021

Accepted 27 July 2021

Keywords:

Covid-19

Bradycardia

Complete atrioventricular block

Transient sinus bradycardia

ABSTRACT

SARS COV-2 infection has become a global threat. Cardiovascular manifestations associated with Covid-19 have been noted in several publications, and bradycardia related to Covid-19 is a commonly reported complication. This study reports six serial cases of bradycardia attributable to Covid-19; four of them developed complete atrioventricular block. These patients experienced clinical symptoms related to bradycardia and initially required permanent pacemaker implantation. However, one patient did not require permanent pacing later on due to spontaneous conversion to sinus rhythm. In comparison, the other two patients who developed transient sinus bradycardia experienced a self-limiting condition during their hospitalization period without requiring any cardiac pacing device or medication to increase heart rate. Complete atrioventricular block and transient sinus bradycardia in these patients, despite not having any history of bradycardia, might be due to complex processes in the systemic inflammatory response in Covid-19. Cardiac monitoring, hemodynamic evaluation, and strategy for permanent pacemaker in these patients should be treated on a case-by-case basis.

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INTRODUCTION

The novel human coronavirus (COVID-19) was first reported in Wuhan, China, and has become the fifth documented pandemic, which has spread worldwide and is currently a global threat. (Yu et al., 2006) Arrhythmic events have become a part of cardiac manifestations related to Covid-19 infection that have been reported in multiple publications. (Xiong et al., 2020, Bansal, 2020, Ulhaq and Soraya, 2020) Bradycardia as a possible clinical feature in Covid-19 hospitalized patients is not well understood but studies suggest that this condition to be due to multiple factors, which include direct myocardial damage, inflammatory response, hypoxia, and down-regulation of angiotensin-converting enzyme-2 (ACE-2). (Blomström-Lundqvist et al., 2020, Gulizia et al., 2020) This study reports the increasing number of symptomatic bradycardia cases related to Covid-19 infection, with no previous history of this condition during this pandemic.

CASE PRESENTATION

Six patients (66.7% women and 33.3% men, with a mean age of 52.16±16.55 years) who were admitted due to a Covid-19 infection and showed respiratory illness, which developed into symptoms related to bradycardia, were identified. All patients were hospitalized at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia during January 2021. All patients were diagnosed with SARS-COV2 infection in accordance with the guideline from the Indonesian Ministry of Health for diagnosing Covid-19, which was by polymerase-chain reaction via a nasopharyngeal swab specimen. All patients were referred from remote areas in South Sulawesi due to limited facilities, and diagnosis confirmation of Covid-19 and symptoms associated with bradycardia was varied for each patient. Types of bradyarrhythmia were recorded using 12-lead electrocardiogram (ECG). Baseline characteristics (patient demographics, clinical findings, laboratory results, and all related data during hospitalization) were collected and can be seen in Table 1.

All patients were southeast Asians, three patients (60%) had comorbidities of hypertension, one patient (20%) had diabetes, one patient (16.7%) was obese with BMI >30 kg/m², none of the patients had a previous history of heart rhythm disorders or coronary

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Table 1
Baseline characteristics.

Baseline characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Demographic						
Age (years)	50	65	43	25	60	70
Gender	Female	Female	Female	Male	Male	Female
Race	Asian	Asian	Asian	Asian	Asian	Asian
BMI (kg/m ²)	31.5	24	21	24	26	22
Comorbidities						
Hypertension	No	Yes	No	No	Yes	Yes
Diabetes	No	Yes	No	No	No	No
Obesity	Yes	No	No	No	No	No
Coronary artery disease	No	No	No	No	No	No
Known arrhythmia disease	No	No	No	No	No	No
Clinical features						
Symptoms related to bradycardia	Yes	Yes	Yes	Yes	Yes	Yes
Respiratory illness	Yes	Yes	Yes	Yes	Yes	Yes
Length of stay (days)	10	12	8	8	10	12
Requiring ICU hospitalization	No	No	No	No	No	No
Requiring mechanical ventilation	No	No	No	No	No	No
Requiring O ₂ supplementation	Yes	Yes	Yes	Yes	Yes	Yes
Hemodynamic instability	Yes	Yes	No	No	No	Yes
Management	Permanent pacemaker	Permanent pacemaker	Temporary pacemaker	Close monitoring	Close monitoring	Permanent pacemaker
Laboratory findings						
D-Dimer (ng/mL – cut-off value 0.5)	6.5	5.4	1.2	1.3	0.8	6.2
Platelets (n x 10 ³)	220	285	322	235	380	188
NLR ratio (%)	7.2	6.7	1.5	1.7	1.65	6.5
Leucocytes (10 ³)	14.8	12.2	7.6	5.6	9.7	12.7
Diagnostic examination						
Chest X-ray	Bilateral pneumonia	Bilateral pneumonia	Normal	Normal	Bilateral pneumonia	Bilateral pneumonia
Echocardiography	No abnormality	No abnormality	No abnormality	No abnormality	No abnormality	No abnormality
Medication						
Anti-arrhythmic agents	No	No	No	No	No	No
Azithromycin	Yes	Yes	Yes	Yes	Yes	Yes
Antiviral (oseltamivir, remdesivir)	Yes	Yes	Yes	Yes	Yes	Yes

artery disease, and none of them were taking any anti-arrhythmic agent. All patients presented clinical symptoms related to bradycardia: lightheadedness, fatigue, near-syncope, and syncope; none required mechanical ventilation.

Laboratory parameters showed that all patients had an increased D-Dimer value that put all at risk of venous thromboembolism. The NLR ratio, leukocytes, and platelets were varied among patients. Interestingly, data revealed that each patient who was implanted with a pacemaker had a higher level of D-Dimer more than three times the upper limit of normal (ULN). Chest X-ray revealed four patients (66.6%) with bilateral pneumonia and two patients (33.3%) were normal. No patients showed cardiac structural abnormality on echocardiography examination. All patients were taking azithromycin and an antiviral agent (oseltamivir or remdesivir) after being diagnosed with Covid-19, and none had a history of taking anti-arrhythmic agents.

All patients were admitted with respiratory illness (cough, dyspnea, fever) and required oxygen supplementation. All patients were referred from remote areas for further examination. On admission, patients underwent a 12-lead ECG. Additional laboratory tests were also conducted, including high-sensitivity cardiac troponin I (hs-TnI), in which all patients showed no increase; therefore, a possible myocardial lesion was excluded.

Patient 1 was shown to have sinus bradycardia with premature atrial complex (PAC) bigeminy, with a previous history of syncope. This patient underwent permanent pacemaker implantation due to hemodynamic instability during hospitalization (Figure 1). Both Patient 2 and Patient 6 were found to have third-degree atrioventricular (AV) block associated with syncope and near-syncope, and

developed hemodynamic instability; they therefore also underwent permanent pacemaker implantation (Figures 2 and 6).

Patient 3 was also found to have developed a third-degree AV block associated with near-syncope but underwent temporary pacemaker prior to transfer to the current hospital and encountered spontaneous resolution on the third day of hospitalization (Figure 3). It was also found that the D-Dimer levels were slightly increased. Patient 4 and Patient 5 were found to have sinus bradycardia with symptoms related to bradycardia. These patients did not develop any hemodynamic instability, gradually showed clinical improvement during hospitalization, and were discharged with an ECG showing regular heart rate without any symptoms (Figures 4 and 5).

Bradycardia attributable to AV block or sinus node dysfunction in these patients required medical attention and close monitoring based on the hemodynamic profiles and ECG results. Patients with persistent complete AV block and sinus bradycardia with hemodynamic instability underwent permanent pacemaker implantation, and those with sinus bradycardia without hemodynamic instability had a self-limiting condition during follow-up.

DISCUSSION

Cardiac arrhythmias, particularly bradycardia, have been noted in several studies and evidence of bradycardia, which is related to infection including severe pneumonia, continue to emerge. (Rivetti et al., 2020, Guo et al., 2020) It is believed that the potential mechanisms of these cardiac arrhythmias include direct myocardial injury, hypoxia, hypotension, enhanced inflammatory re-

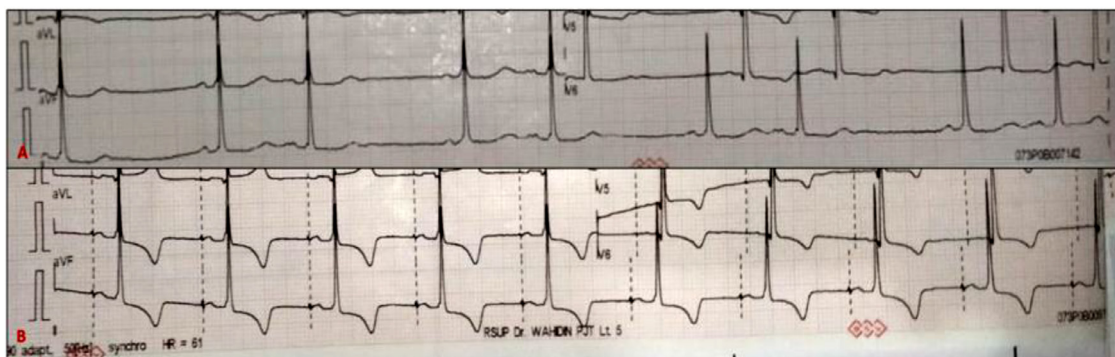


Figure 1. Patient 1 (baseline ECG and on discharge). Baseline ECG report from Patient 1 showing sinus bradycardia with premature atrial complex bigeminy (A); ECG on discharge showing atrial pacing rhythm and ventricular sensing (B)

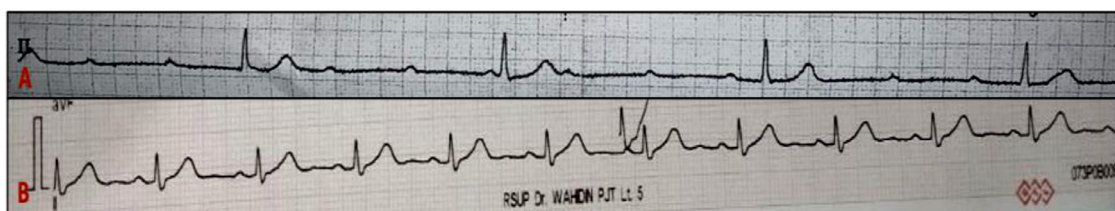


Figure 2. Patient 2 (baseline ECG and on discharge). Baseline ECG report from Patient 2 showing third-degree AV block with ventricular rate 25 bpm (A); ECG on discharge showing atrial pacing rhythm and ventricular sensing with heart rate 70 bpm (B)

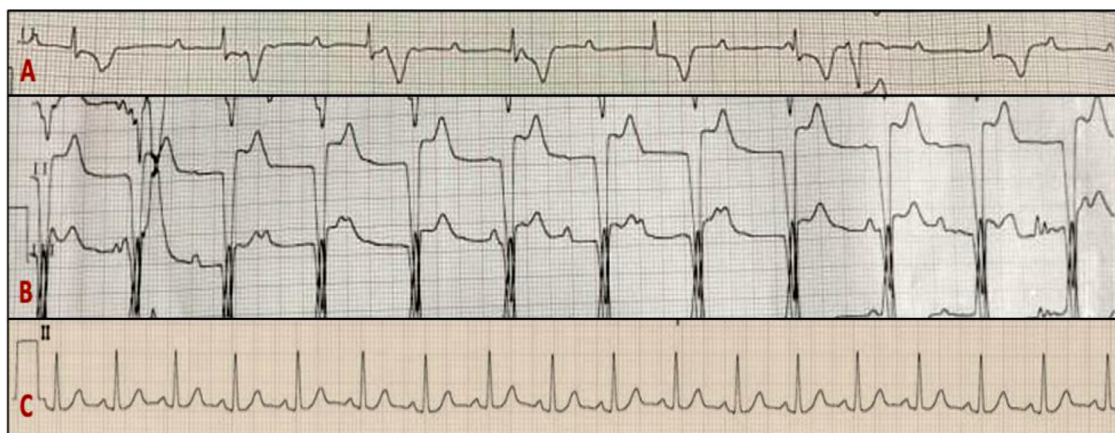


Figure 3. Patient 3 (baseline ECG and on discharge). Baseline ECG report from Patient 3 showing third-degree AV block with ventricular rate 46 bpm (A); ECG on temporary pacemaker showing ventricular pacing rhythm with heart rate 65 bpm (B); three days after temporary pacemaker, the ECG showed spontaneous resolution to sinus rhythm with heart rate 100 bpm (C)



Figure 4. Patient 4 (baseline ECG and on discharge). Baseline ECG report from Patient 4 showing sinus bradycardia with heart rate 46 bpm (A); ECG on discharge showing sinus rhythm with heart rate 60 bpm (B)



Figure 5. Patient 5 (baseline ECG and on discharge).

Baseline ECG report from Patient 5 showing sinus bradycardia with heart rate 39 bpm (A); ECG on discharge showing sinus rhythm with heart rate 62 bpm (B)



Figure 6. Patient 6 (baseline ECG and on discharge).

Baseline ECG report from Patient 6 showing third-degree AV block with ventricular rate 41 bpm (A); ECG on discharge showing atrial pacing rhythm and ventricular sensing with heart rate 60 bpm (B)

sponse, and ACE-2 receptor down-regulation. (Gulizia et al., 2020, Kochav et al., 2020) Pro-inflammatory indicators such as IL-6 and D-dimer levels are thought to play a role in the systemic inflammation of Covid-19 and contribute to the cardiac manifestation of Covid-19 itself. (Blomström-Lundqvist et al., 2020, Liu et al., 2020)

Five of these patients showed increased D-dimer levels, which put them in a pro-inflammatory state. The European Society of Cardiology has guided permanent pacemaker implantation in patients with complete AV block associated with Covid-19. It should be implemented until the patient is afebrile for more than 24 hours. (Hu et al., 2020) In contrast, the Italian Association of Hospital Cardiologists (ANMCO) has released a position paper recommending an early permanent pacemaker implantation rather than a temporary pacemaker due to the risk of infection. (Amaratunga et al., 2020) The current hospital implemented permanent pacemaker implantation due to documented complete AV block with hemodynamic instability and a history of pre-syncope and syncope. Other considerations to implementing a permanent pacemaker were minimizing the time of exposure and reducing hemodynamic consequences; in addition, viral diseases have rarely been associated with cardiac implantable electronic device (CIED) infection. (Hu et al., 2020, Liu et al., 2020) Transient sinus bradycardia in the current patients was a self-limiting condition, which did not require any CIED or medication to increase heart rate.

This study reports short-term evaluation on symptomatic bradycardia patients with Covid-19. Further research on other aspects such as long-term patient outcomes is needed to establish a better understanding of this condition.

CONCLUSION

This study reported a case series of bradycardia associated with SARS COV-2 infection during the COVID-19 pandemic. The patients had either developed complete AV block or transient sinus bradycardia without previously documented bradycardia, which might have been due to a complex process in a systemic inflammatory response to Covid-19. During this pandemic, patients who develop cardiac rhythm disturbances associated with respiratory illness should be suspected as having SARS COV-2 infection, mainly in remote areas with limited resources. Cardiac monitoring, hemodynamic evaluation, and a strategy for permanent pacemaker in these patients should be treated on a case-by-case basis. Cardiac arrhythmia is one of several other cardiac manifestations of SARS-COV2 infection and is presumed to be a multifactorial condition. These cardiac electrical disturbances in Covid-19 patients should lead to further enhanced electrophysiology study and other diag-

nostic methods to understand the underlying and exact pathomechanism of arrhythmias in SARS-COV 2 infection.

Conflict of Interest

The authors do not have a conflict of interest to disclose.

Funding Source: This research received no specific funding.

Ethics approval and consent to participate: Informed consent was obtained from all individual participants included in the study.

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