Theophylline to treat prolonged paroxysmal complete atrioventricular block without conduction disorder or structural heart disease after COVID-19 infection: A case report

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Introduction

The novel coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense, single-stranded RNA virus. The most common symptoms include cough, fever, fatigue, shortness of breath, sore throat, and headache. Although respiratory failure is the primary complication seen in COVID-19 patients, the cardiovascular system can also be targeted with complications, including myocardial injury, myocarditis, arrhythmias, heart failure, and acute myocardial infarction. Some COVID-19 patients go into an advanced-degree heart block and suffer cardiac arrest related to complete heart block.[1] Here, we describe a case of paroxysmal complete atrioventricular (AV) block in a patient with COVID-19.

Case report

A 43-year-old man with a history of essential hypertension and hyperuricemia presented with fever, cough, and diarrhea for 1 week. His home medications included 5 mg of amlodipine, 80 mg of valsartan, and 20 mg of febuxostat once daily. His body mass index was 27.5. He underwent a medical checkup annually and had never been diagnosed with any heart disease or had an abnormal electrocardiogram (ECG). Two days before the current presentation, he tested positive for COVID-19 via a polymerase chain reaction test. He presented to the emergency department with worsening dyspnea. In the emergency department, his vital signs were as follows: body temperature, 38°C; pulse rate, 125 beats per minute; blood pressure, 136/89 mm Hg; respiratory rate, 28 respirations/minute; and oxygen saturation, 94% on 2 L nasal cannula oxygen. Chest radiography showed bilateral ground-glass opacity. The ECG on admission revealed sinus rhythm without any ST-T wave changes or conduction disorder (Figure 1).

He was started on a combination treatment of remdesivir and dexamethasone by intravenous infusion. Remdesivir was started on day 1 of hospitalization with a loading dose of 200 mg on day 1 and 100 mg daily for 4 additional days. He was started on dexamethasone 6 mg daily for 10 days.

KEY TEACHING POINTS

- Atrioventricular (AV) block can present in COVID-19 regardless of the history of conduction disease, and the course can be either intermittent or progressive. It can recover spontaneously or persist.
- Daily electrocardiograms and close surveillance of patients who develop severe bradycardia or AV block are essential.
- The pathogenesis of AV block remains poorly understood. Some proposed mechanisms include direct COVID-19 involvement to the heart's conduction system, COVID-19 myocarditis, and the cardiac toxicity associated with remdesivir.
- Oral theophylline can be an effective treatment alternative to permanent pacemaker insertion. Theophylline therapy may be considered in a case with a tendency to recover.

KEYWORDS AV block; COVID-19; Remdesivir; ATP; Adenosine; Theophylline

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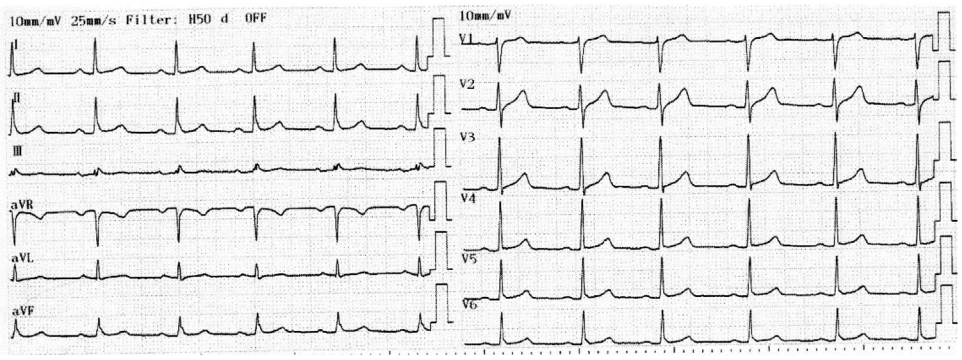

Figure 1 The patient's initial electrocardiogram showed sinus rhythm with a heart rate of 69 beats per minute. The PQ interval was 164 ms. There was no bundle branch block or conduction disorder.

After 4 days of remdesivir administration, on the early morning of the fifth day of hospitalization, the ECG demonstrated paroxysmal complete AV block (Figure 2). AV block was first noticed early in the morning when the patient was asleep and did not have syncope. The second time, AV block was identified for 5 seconds during the day with presyncope. Brain natriuretic peptide and troponin T levels were normal. Transthoracic ultrasonic echocardiography and cardiac magnetic resonance imaging showed no organic abnormalities or evidence of myocarditis due to COVID-19 infection.

On day 5, he underwent temporary transvenous pacemaker implantation in VVI mode at 40 beats per minute, and remdesivir therapy was discontinued. The number of AV block events decreased as he recovered from the COVID-19 infection and remdesivir's concentration fell beyond its half-life. However, on day 13, AV blocks were observed more than 20 times per day. AV block in this case was characterized by a sudden onset of complete AV block without changes in P-P cycle length, long ventricular asystole of approximately 5 seconds, and spontaneous return to sinus rhythm. Because we diagnosed this case as adenosine-sensitive AV block, we administered 200 mg of oral theophylline, an adenosine antagonist, twice daily. After administration of theophylline, the frequency of AV block decreased without an increase in the heart rate. The AV block was not observed for 3 days; therefore, on day 21, the temporary external pacemaker was removed (Figure 3). A few seconds of AV block was seen once at dawn on days 22 and 23, but the patient did not experience syncope or faintness. We implanted an implantable loop recorder to continue monitoring on day 22, and he was discharged on day 23. According to the remote monitoring data, the paroxysmal AV block event has been confirmed about once a month. All AV block events occurred early in the morning and did not have syncope.

Discussion

COVID-19 is caused by SARS-CoV-2. The SARS-CoV-2 invades cells through angiotensin-converting enzyme 2 receptors found in the lung and heart tissues.[2] Respiratory illness is a well-known manifestation of COVID-19, but cardiac involvement has also been reported in the literature, ranging from asymptomatic myocardial injury to acute coronary syndrome, myocarditis, stress cardiomyopathy, cardiogenic shock, and cardiac arrhythmias.[3] A few cases of complete AV block in patients with COVID-19 have been reported recently. It has also been reported in patients with and without preexisting conduction disease.[1,3,4] Our patient did not show signs of having any reversible causes for his AV block, such as thyroid dysfunction, electrolyte disturbances, or acute myocardial infarction. He did not have extensive systemic or myocardial involvement.

The pathogenesis of AV block remains poorly understood; however, multiple proposed mechanisms include direct COVID-19 involvement in the heart's conduction system, COVID-19 myocarditis, and cardiac toxicity associated with remdesivir.

The COVID-19 infection is accompanied by an aggressive inflammatory response with the release of a large amount of proinflammatory cytokines like TNF-α, IL-1, and IL-6, known as "cytokine storm." Lazzerini and colleagues[5] suggested that inflammatory cytokines can modulate the expression and function of ion channels by acting directly on cardiac myocytes and indirectly through systemic effects, perhaps leading to conduction disturbances. Others[6,7] report

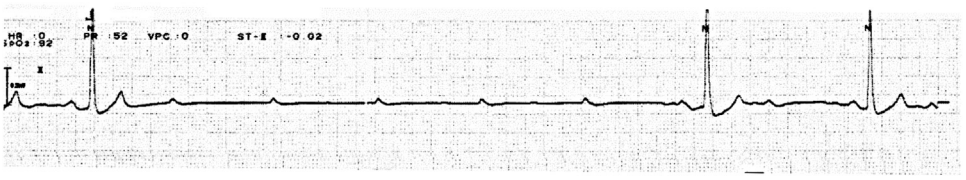

Figure 2 Single-channel electrocardiogram recorded from the bedside monitor showed paroxysmal atrioventricular block without changes in P-P cycle length, which constantly remained 120 ms, and long ventricular asystole 6.6 seconds.

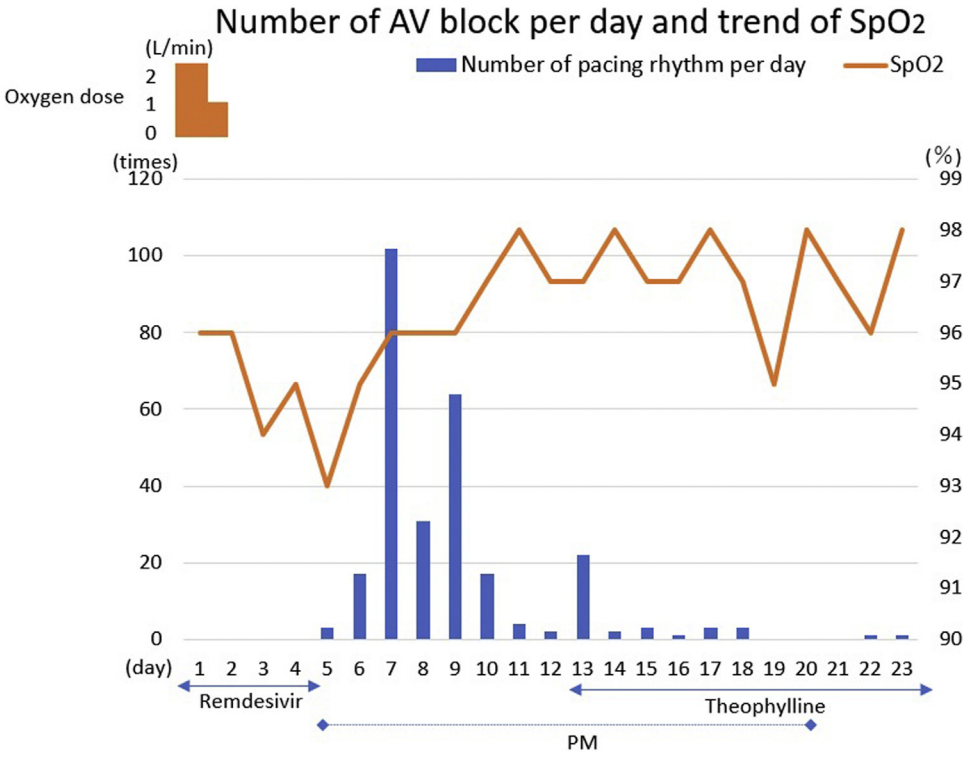

Figure 3 On day 5, a temporary transvenous pacemaker (tPM) was implanted, and remdesivir therapy stopped. On day 13, we prescribed 200 mg of theophylline. Theophylline treatment reduced the number of atrioventricular (AV) block episodes. On day 21, the tPM was removed.

that direct involvement of the AV node by SARS-CoV-2, as studied in animal models, has shown the presence of angiotensin-converting enzyme 2 receptors throughout the conduction system.

Viral infections are considered one of the most common infectious causes of myocarditis. Whether the development of arrhythmia is secondary to direct viral involvement or due to an exaggerated inflammatory response remains unknown. Our patient had no elevated troponin levels, no abnormal findings on magnetic resonance imaging, and no complications of myocarditis.

Remdesivir is an internationally approved broad-spectrum antiviral drug that has shown promising results in treating COVID-19-related lower respiratory infections.[8] Remdesivir is a prodrug that is subsequently metabolized to nucleoside triphosphate via enzymatic reactions once transported intracellularly. The metabolite form inhibits the function of the polymerase responsible for transcription and replication of the genome, thereby suppressing viral replication.[9] One of the leading theories of how remdesivir can induce sinus node and AV node dysfunction is based on its active metabolized triphosphate form and its close structural resemblance to adenosine 5-triphosphate (ATP).[10] The ATP and its metabolized form of adenosine are known to exert negative chronotropic and dromotropic effects on sinus node automaticity and AV nodal conduction. This effect is mediated by ATP's ability to suppress the sinus and AV nodes by transiently enhancing vagal tone in the heart.[11] The effect of adenosine on the AV node is mainly due to the stimulation of high-affinity A1 receptors, which are much more numerous in the AV node than in the sinoatrial node. Therefore, it can be postulated that the remdesivir metabolite may exert the same deleterious effects on the conduction system. Another mechanism possibly relates to remdesivir's affinity toward RNA polymerases and subsequent mitochondrial dysfunction, resulting in cardiotoxicity. The pharmacologically active triphosphate form has a half-life of 11 hours, and there is another dephosphorylated nucleoside metabolite with a half-life of 20–25 hours. The timing of the AV block in our case indicates a contribution from remdesivir. The AV block did not completely disappear after remdesivir discontinuation, but the frequency decreased.

Paroxysmal AV block is characterized by the sudden appearance of a complete heart block. The mechanism of the idiopathic paroxysmal AV block remains unclear. Recently, the role of lower baseline adenosine levels and excessive susceptibility to exogenous adenosine has also been suggested.[12]

Blood adenosine levels were not measured in our patient. However, there was a possibility of potentially low endogenous adenosine and excessive susceptibility to exogenous adenosine owing to remdesivir. Theophylline is an adenosine antagonist that has been identified as a treatment option for bradyarrhythmic events. In 2 recent small observational studies, oral theophylline appeared to be effective over a mean follow-up period of 16 and 17 months in patients with an established diagnosis of idiopathic paroxysmal AV block and may be considered an alternative to permanent pacing in such patients.[13] In this case, we think oral theophylline may be effective, avoiding permanent pacemaker insertion in the acute phase.

However, AV blocks without any symptoms were occasionally observed even after theophylline was started. These AV block events only occurred during sleep, and his simplified polysomnography showed an apnea-hypopnea index of 17.2/hour and minimum oxygen saturation 78%. Therefore, we think they were related to sleep apnea syndrome.[14,15]

Conclusion

An AV block is present in SARS-CoV-2-infected patients regardless of the history of conduction disease. Daily ECGs and close surveillance are essential for patients with COVID-19. The AV block may resolve with recovery from COVID-19, and pharmacotherapy may be an alternative treatment for pacemaker implantation. In the present case, theophylline therapy was beneficial. The prognosis and cause of AV block in COVID-19 remain unknown. Further research is needed to characterize the mechanism of injury and arrhythmia burden to guide the development of therapies.

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