Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Potentially fatal severe brady arrythmias related to Lopinavir-Ritonavir in a COVID 19 patient

Dear Editor,

The novel coronavirus (COVID-19) outbreak was declared a global pandemic, with over 6 million people infected, and 371,166 deaths worldwide. Without proven treatments for severe COVID-19, physicians have resorted to experimental therapies like Lopinavir-Ritonavir.[1,2] We report the first case of potentially fatal bradyarrhythmias with long sinus pauses due to Lopinavir-Ritonavir.

The patient is a 67-year-old male with a history of hypertension and coronary artery disease. He tested positive for COVID-19 on day 5 of respiratory symptoms. On day 10, he deteriorated and Lopinavir 4 mg/kg/Ritonavir 1 mg/kg 12-hourly was initiated. His baseline electrocardiogram showed a heart rate of 84 bpm, and QTc of 496 ms.

On day 12, he developed moderate acute respiratory distress syndrome requiring intubation and mechanical ventilation. He was subsequently sedated with IV propofol (2—2.5 mg/kg/h) and fentanyl (1-1.5 mcg/kg/h).

On day 15, he developed episodes of sinus pauses, longest recorded was 3.8s with spontaneous recovery. Hours later, he developed sustained significant bradycardia (30 bpm) with severe hypotension (systolic blood pressure 50 mmHg) (Fig. 1a and b). He was given intravenous ephedrine 20 mg and atropine 1200 mcg, and was subsequently started on intravenous dopamine 5 mcg/kg/min. Transcutaneous pacing pads were applied with a backup rate of 50 bpm. A transthoracic echocardiogram showed a normal ejection fraction. Throughout the day, we observed multiple bradycardic episodes requiring backup pacing (Fig. 1c). Lopinavir-Ritonavir was discontinued.

After cessation of Lopinavir-Ritonavir, no further episodes of bradyarrhythmias were observed. Dopamine was weaned off over 48 h, and his heart rate remained stable. He made a full recovery subsequently.

Lopinavir-Ritonavir is the most common protease inhibitor listed for investigational or compassionate use for COVID-19 in international clinical guidelines. However, current evidence on the efficacy and safety of any protease inhibitors for treating COVID-19 infection is debated.[1,2] Despite some recommendations that Lopinavir-Ritonavir should be started early,[2] there are side effects that should be weighed cautiously.

Differential causes of bradyarrhythmias, including hypoxia, propofol infusion syndrome, myocarditis, and acute coronary events, should be excluded. Throughout the event, our patient showed no ischemic changes on the electrocardiogram, and highest QTc was 491 ms. Echocardiogram and investigations were unremarkable.

We suggest pre-emptive placement of transcutaneous pacing in COVID-19 patients with significant arrhythmias. This could be life-saving as delays in attending to emergencies are expected, due to the need to don personal protective equipment.

Lopinavir-Ritonavir blocks human ether-a-go-go-related gene potassium channels, predisposing to QTc prolongation.[3] Although our patient had a baseline prolonged QTc, it was not exacerbated by Lopinavir-Ritonavir. Predisposition to arrhythmias have been postulated to be caused by genotype polymorphisms (e.g. HCN4 genes) coding for the sinus node,[4] exacerbated by drugs. Future phenotype studies in such patients can be explored.

Second- and third-degree heart blocks have been reported previously in HIV patients taking Lopinavir-Ritonavir.[5] However, this is the first reported case of sinus pauses requiring transcutaneous pacing in a COVID-19 patient. Jimenez et al. reported a patient who developed complete atrioventricular block and asystole. Kikuchi et al. reported two cases of Mobitz type-I block and sinus arrest with junctional escape rhythm.[5]

We recommend caution in starting Lopinavir-Ritonavir, especially in patients with cardiovascular co-morbidities.

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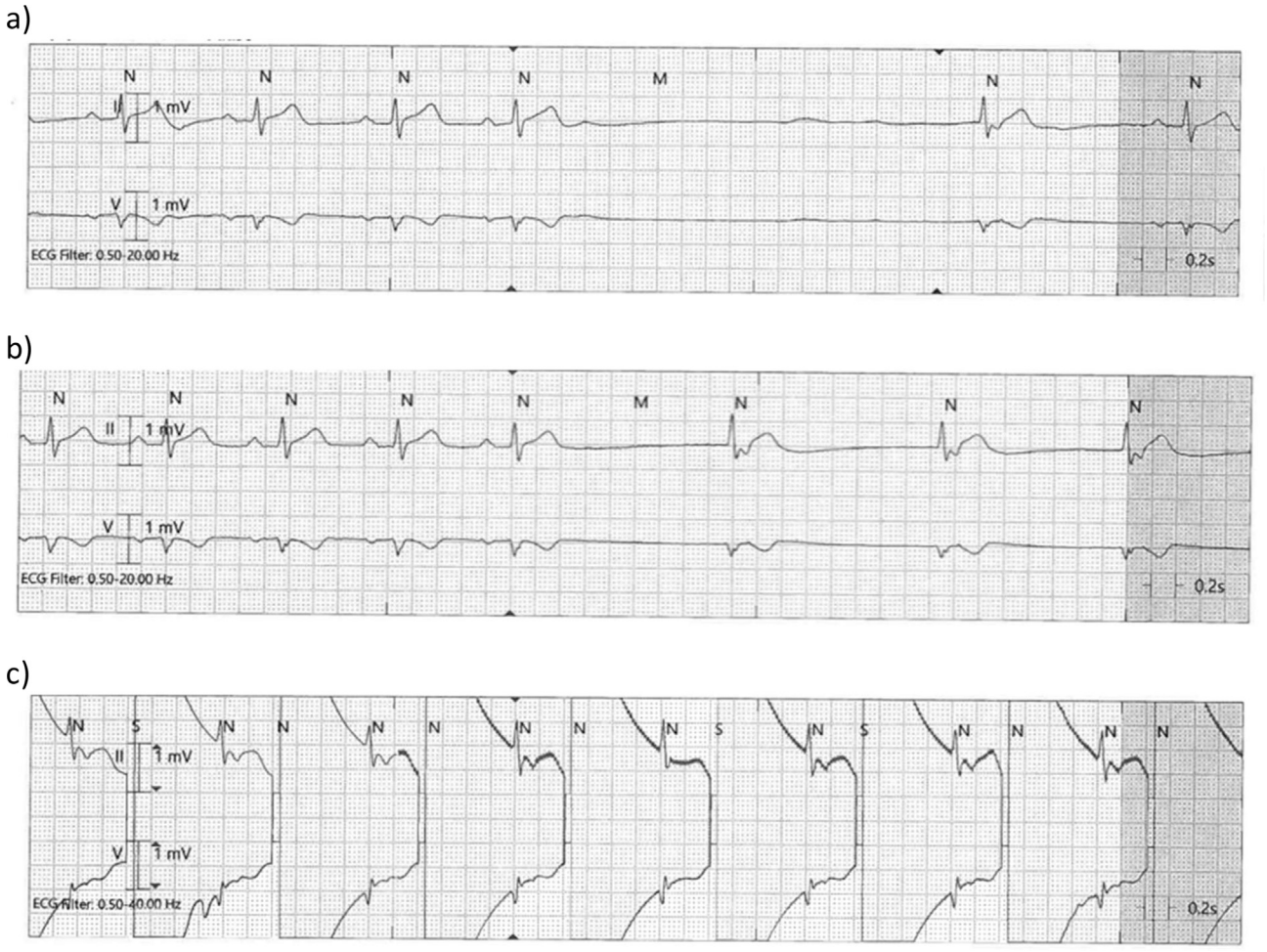

Figure 1. Electrocardiograms a), b) illustrating severe bradycardia and sinus pauses, and c) illustrating backup paced rhythms.

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References

1. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir—ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020 Mar 18;**382**:1787—99. https://doi.org/10.1056/NEJMoa2001282.
2. Owa AB, Owa OT. Lopinavir/ritonavir use in Covid-19 infection: is it completely non-beneficial? *J Microbiol Immunol Infect* 2020 May 25. https://doi.org/10.1016/j.jmii.2020.05.014.
3. Anson BD, Weaver JG, Ackerman MJ, Akinsete O, Henry K, January CT, et al. Blockade of HERG channels by HIV protease inhibitors. *Lancet* 2005 Feb 19;**365**(9460):682—6.
4. Schulze-Bahr E, Neu A, Friederich P, Kaupp UB, Breithardt G, Pongs O, et al. Pacemaker channel dysfunction in a patient with sinus node disease. *J Clin Invest* 2003;**111**:1537—45.
5. Chaubey SK, Sinha AK, Phillips E, Russell DB, Falhammar H. Transient cardiac arrhythmias related to lopinavir/ritonavir in two patients with HIV infection. *Sex Health* 2009 Aug 24;**6**(3):254—7.

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