

A case report of severe cardioinhibitory reflex syncope associated with coronavirus disease 2019

Johannes Beil , Alessia Gatti , Bruch Leonhard , and Hinrich Schroer *

Department of Internal Medicine/Cardiology, BG Klinikum Unfallkrankenhaus Berlin, Warener Str. 7, 12683 Berlin, Germany

Received 22 April 2021; first decision 7 June 2021; accepted 20 December 2021; online publish-ahead-of-print 3 January 2022

Background

Coronavirus disease 2019 (COVID-19) has been recognized as a disease with a broad spectrum of clinical manifestations. In this report, we illustrate an extraordinary case of severe cardioinhibitory reflex syncope with prolonged asystole associated with COVID-19.

Case summary

A 35-year-old male patient presented to the emergency department with a 10-day history of postural syncope and fever. Electrocardiogram monitoring during positional change revealed reflex syncope with cardioinhibitory response, exhibiting sinus bradycardia, subsequent asystole, and syncope. The patient tested positive for severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and was admitted to the intensive care unit where temporary transvenous pacing was necessary because of prolonged episodes of asystole. Work-up included extensive cardiac and neurological diagnostic testing, but did not yield any structural abnormalities. Although temporary pacing was able to abort syncope, a decision was made to hold off on permanent pacing as the most likely aetiology was felt to be temporary cardioinhibitory reflex syncope associated with COVID-19. The patient was discharged with mild symptoms of orthostatic intolerance and responded well to education and lifestyle modification. Outpatient follow-up with repeat tilt testing after 3 and 6 months initially showed residual inducible syncope but was eventually normal and the patient remained asymptomatic.

Discussion

We believe that autonomic imbalance with a strong vagal activation due to acute SARS-CoV-2 infection played a pivotal role in the occurrence of transient syncope in this patient's condition. Although pacemaker implantation would have been a reasonable alternative, a watch-and-wait approach should be considered in similar instances.

Keywords

COVID-19 • Cardioinhibitory reflex syncope • Pacemaker • Case report

ESC Curriculum

5.7 Bradycardia • 5.9 Pacemakers • 5.2 Transient loss of consciousness

Learning points

- Autonomic dysfunction could be a manifestation of coronavirus disease 2019 (COVID-19).
- Autonomic dysfunction can resolve slowly.
- A wait-and-see approach in cardioinhibitory reflex syncope with COVID-19—given its transient course—should be considered.

Introduction

More than 1 year into the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) pandemic, our knowledge regarding clinical manifestations of coronavirus disease 2019 (COVID-19) expands. There is growing evidence that COVID-19 is a systemic disease with various manifestations, rather than an isolated respiratory disease.^{1,2} Herein, we present a case of severe cardioinhibitory reflex syncope associated with COVID-19.

* Corresponding author: Tel: +49 30 5681 3601, Email: hinrich.schroer@ukb.de

Handling Editor: Ruben Casado Arroyo

Peer-reviewers: Goksel Cinier; Richard Ang; Abdullah Sayied Abdullah; Fabian Barbieri and Markus Bettin

Compliance Editor: Linh Ngo

Supplementary Material Editor: Fabienne Vervaat

© The Author(s) 2022. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Timeline

Day 0	Onset of syncopal episodes on positional change from supine to sitting
Day 9	Febrile temperatures noted by patient
Day 10	Admission to hospital Electrocardiogram (ECG) documentation of asystole Laboratory blood test results showed typical changes consistent with viral infection Positive severe acute respiratory syndrome coronavirus type 2 test
Day 11	Transthoracic echocardiogram showed normal heart structure Computed tomography chest showed bilateral, patchy opacities consistent with coronavirus disease 2019 (COVID-19) Intensive care unit admission Lumbar puncture ruled out COVID-19- related central dysautonomia 24-h Holter ECG showed pauses with a maximum duration of 3.4 s during sinus arrest and episodes of idioventricular rhythm as well as a single episode of slow-ventricular tachycardia over 35 s Initiation of antibiotic therapy with Piperacillin/Tazobactam and Azithromycin
Day 12	Episodes of asystole while supine Placement of temporary transvenous pacemaker
Day 16	Second 24-h Holter ECG without relevant arrhythmia Removal of temporary pacemaker due to recovered intrinsic rhythm Cardiac magnetic resonance imaging without any structural abnormalities
Day 29	Hospital discharge
Three months	Typical cardioinhibitory pattern with asystole during tilt testing
Six months	Normal tilt test Patient asymptomatic

Case presentation

A 35-year-old male patient presented to the emergency department with a 10-day history of syncope occurring on positional change from supine to a sitting position. One day prior to presentation, the patient had experienced a first episode of fever around 39°C. He denied dyspnoea or cough. Neither sitting nor standing was possible due to transient loss of consciousness. Initial provocative testing in the emergency department showed that upon assuming an upright, seated position, there was an initial rise in heart rate to 110 b.p.m. in sinus rhythm. The patient was normotensive. Within the following 2–3 min, there was a slow decline in heart rate and eventually onset of sinus bradycardia. With onset of marked bradycardia, the patient was

yawning and complaining of dizziness and visual blurring, followed by syncope. Other typical prodromal symptoms were not noted. There was no PR prolongation during these episodes and no evidence of AV conduction abnormalities (Figure 1). Previous medical history had been unremarkable except for asthma treated with salbutamol as required. There was no family history of unexplained syncope or unexplained sudden cardiac death. Our patient reported no history of syncope, including syncope related with febrile illness.

On examination, the patient exhibited bilateral basal crackles on auscultation, febrile body temperatures (39°C) and tachycardia (107 b.p.m.). Blood pressure, respiratory rate, and peripheral oxygen saturation were normal. Arterial blood gas sampling showed mild hypoxaemia (pO₂: 10.1 kPa; reference range: 11.0–14.4 kPa). Laboratory results showed raised C-reactive protein (32.9 mg/L), Procalcitonin (0.10 µg/L), Ferritin (1874 µg/L), mildly raised aminotransferases (ALAT: 0.86 µkat/L, ASAT: 1.05 µkat/L) as well as leukopenia (3.7 Gpt/L). Hs-troponin T and thyroid-stimulating hormone were within normal range.

The patient tested positive for SARS-CoV-2 on a nasopharyngeal swab and subsequent chest computed tomography showed bilateral, patchy opacities consistent with COVID-19 (Figure 2). Severe acute respiratory syndrome coronavirus type 2 antibodies were negative.

The patient was admitted to intensive care unit (ICU) and antibiotic treatment with Piperacillin/Tazobactam was initiated. A 24-h Holter electrocardiogram (ECG) and a transthoracic echocardiogram were performed. Holter ECG showed two pauses with a maximum duration of 3.4 s during sinus arrest, episodes of idioventricular rhythm as well as a single episode of slow-ventricular tachycardia over 35 s. Transthoracic echocardiogram revealed a normal left ventricular ejection fraction without any structural abnormalities. A lumbar puncture to rule out COVID-19-related central dysautonomia—i.e. Guillain-Barré syndrome—did not reveal any abnormalities. Oxygen saturation remained stable; consequently, our patient did not receive immunomodulatory therapy with dexamethasone.

Due to recurrent episodes of prolonged asystole after admission to ICU, a decision was made to place a temporary transvenous pacemaker via the right internal jugular vein to enable mobilization. Following pacemaker placement, syncope stopped.

After a further 5 days, a repeat 24-h Holter ECG no longer showed evidence of ventricular pacing following positional change (Figure 3). Therefore, the temporary pacemaker was removed. Subsequent cardiac magnetic resonance imaging was performed and did not reveal structural heart disease (Figure 4). The patient was transferred to a telemetry ward for the remainder of the acute phase of COVID-19. He was discharged after 29 days of inpatient care with occasional symptoms of orthostatic intolerance and responded well to lifestyle modification and education. This included instructions on recognizing prodromal symptoms and measures to prevent traumatic injury secondary to syncope. Also, since the patient was a keen cyclist, we suggested refraining from cycling until resolution of symptoms. Inpatient stay was prolonged due to regulations regarding safe discharge of COVID-19 patients.

Three months after the initial hospitalization the patient reported only mild episodes of pre-syncope. However, tilt testing still showed evidence of cardioinhibitory reflex syncope (Figure 5A).

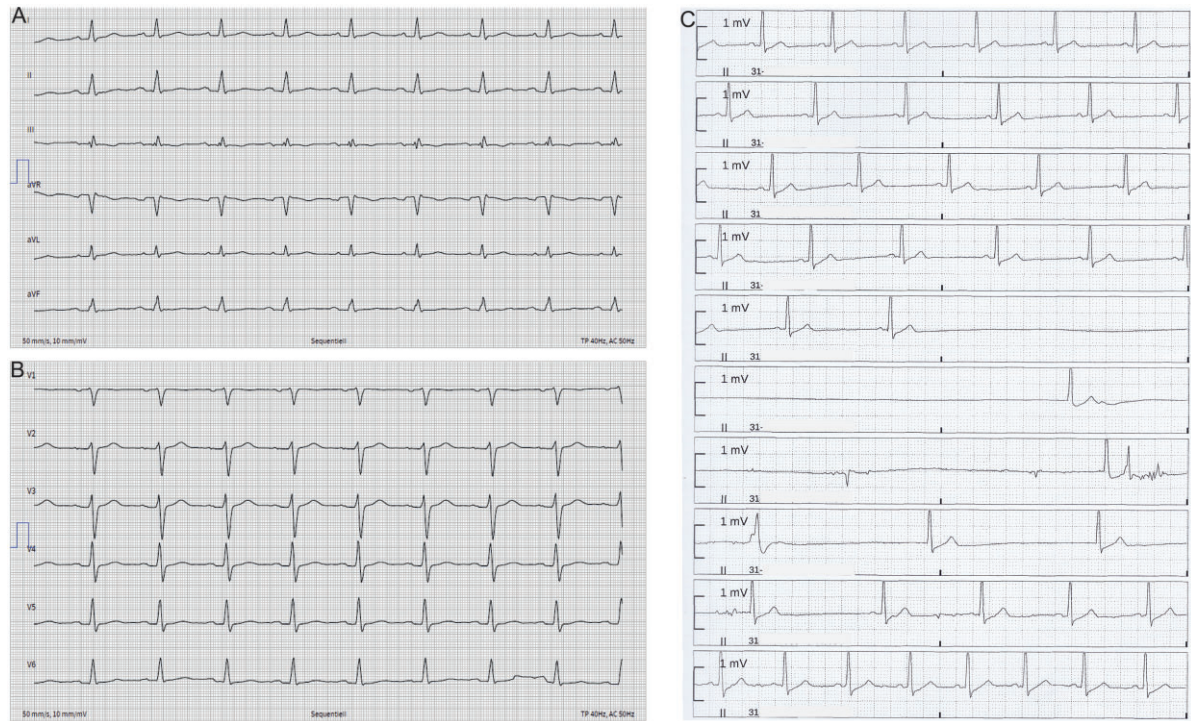


Figure 1 Electrocardiogram at initial presentation. Twelve-lead electrocardiogram (A, B) showing sinus tachycardia (paper speed 50 mm/s). Telemetry rhythm strip (C) during episode of postural syncope showing sinus bradycardia and asystole with a 7.76 s pause (paper speed 25 mm/s). Note the typical pattern of cardioinhibitory response with sinus bradycardia leading to sinus arrest and asystole.

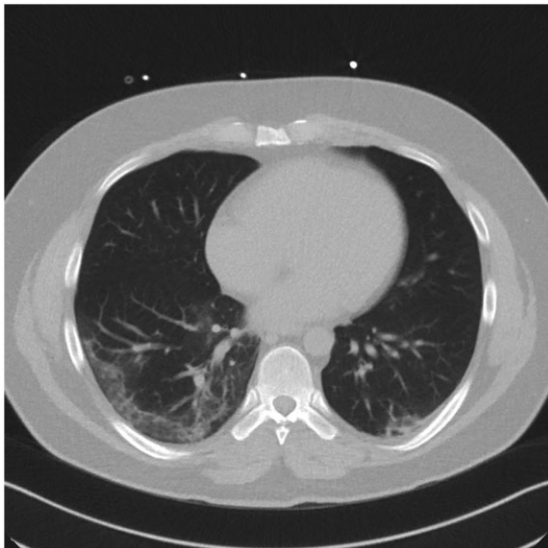


Figure 2 Chest computed tomography on admission showing bilateral, patchy ground-glass opacification consistent with pulmonary involvement in coronavirus disease 2019.

On a final outpatient follow-up almost 6 months after the initial presentation, the patient reported to be free of syncopal and pre-

syncopal symptoms, with further tilt testing showing no abnormalities at all (Figure 5C and D). Laboratory results confirmed a high antibody titre against SARS-CoV-2.

Discussion

This report illustrates the case of a patient with transient severe syncope with cardioinhibitory response associated with COVID-19. Differential diagnoses in this patient include inherited channelopathies such as Brugada syndrome or paroxysmal AV block. However, due to the reproducible circumstances during which syncope manifested, a clear chronological correlation between symptoms and SARS-CoV-2 infection and the lack of features suggesting channelopathies or structural heart disease, we believe that cardioinhibitory reflex syncope associated with COVID-19 is the diagnosis in this patient.

Multiple reports have emerged, suggesting implication of the autonomous nervous system^{3,4} as well as the cardiovascular system⁵ in COVID-19. Especially in ‘long COVID’, orthostatic intolerance has been described.⁶ Postural tachycardia syndrome—being one of the orthostatic intolerance syndromes—can regularly be found in cases of COVID-19.⁷ A case series with seven patients has shown that syncope can be a presenting symptom of COVID-19.⁸ However, in a recent retrospective analysis of consecutive patients hospitalized with laboratory-confirmed COVID-19, syncope seemed to be uncommon.⁹

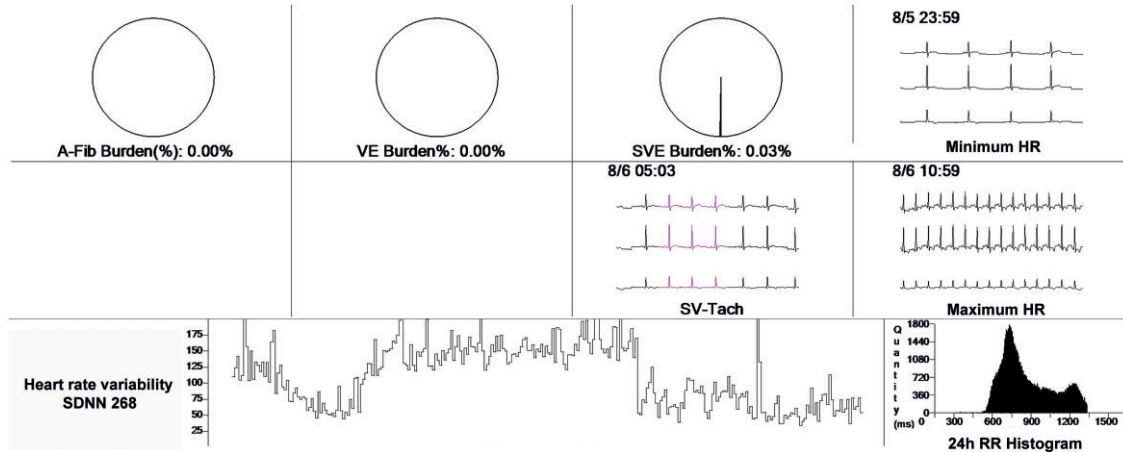


Figure 3 Representative 24-h Holter recording. Twenty-four-hour Holter at 6 days after admission showing no evidence of atrial fibrillation (A-Fib) or ectopics (VE Burden, SVE Burden) or ventricular pacing. Also, note high SDNN of heart rate variability. SDNN, standard deviation of normal-to-normal RR intervals.

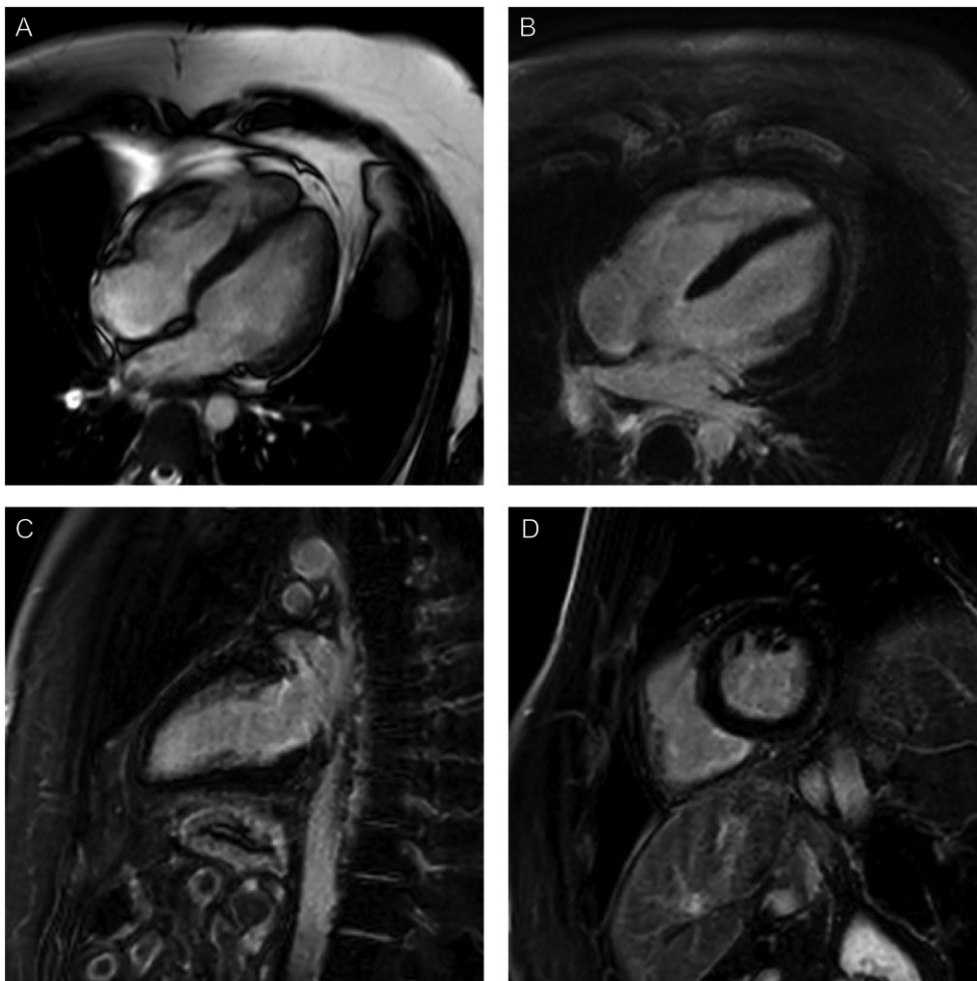


Figure 4 Representative cardiac magnetic resonance images. Four-chamber view (cine steady-state free precession imaging sequence) showing normal-sized ventricles (A). No evidence of late gadolinium enhancement on T1-weighted four-chamber, two-chamber, and short-axis views (B–D).

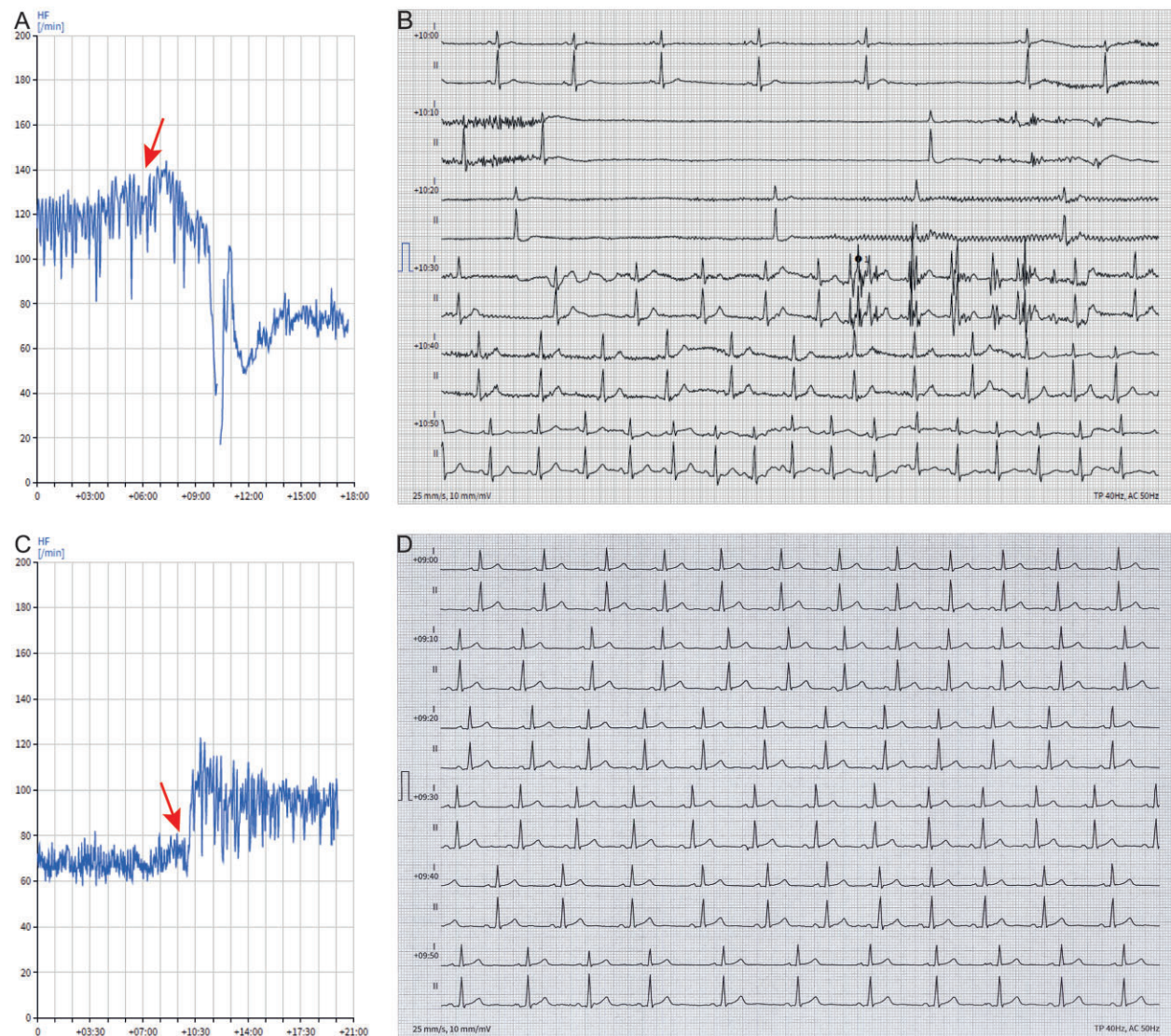


Figure 5 Tilt testing at different time intervals during the course of illness. Red arrows indicating positional change to upright position. Tilt testing (A) at 3 months after symptom onset showing initial physiological rise in heart rate of <math><30\text{ b.p.m.}</math>, followed by progressive bradycardia and asystole with a 5.2 s pause (B). Normal tilt testing (C, D) at 6 months after onset of symptoms.

Two different mechanisms of interaction between COVID-19 and the autonomic nervous system have been proposed. Firstly, a cytokine response following SARS-CoV-2 infection may lead to sympathetic activation. In contrast, a strong vagal stimulation results in an anti-inflammatory response.¹⁰ A strong activation of the vagal nerve, which balances cytokine production, has already been described in other infectious diseases and has been termed ‘the theory of the cholinergic anti-inflammatory pathway’.¹¹ It has also been hypothesized that autonomic balance determines the severity of COVID-19. A depressed vagal tone in COVID-19 seems to be a predictor of a worse outcome.¹²

On the other hand, the virus itself could mediate an autonomic imbalance as described in immune-mediated neurological syndromes.¹³ Although the exact mechanism still remains uncertain, both seem to

have a transient nature in common. We believe it is conceivable that a strong vagal activation in response to infection with SARS-CoV-2 could have played a role in promoting cardioinhibitory syncope.

Although our patient had severe symptoms with a high frequency of syncope and long pauses in asystole, a deliberate decision was made to hold off on permanent pacing. This decision was based on the identification of COVID-19 as a transient trigger mechanism, and on the background of European Society of Cardiology (ESC) Guidelines on syncope giving a class IIA recommendation for pacemaker implantation in cardioinhibitory reflex syncope in patients above 40 years, and therefore older than our patient.¹⁴ The Task Force of the latest ESC Guidelines on cardiac pacing has even found sufficient evidence in the literature to recommend pacing with a class IA recommendation in highly selected patients with reflex syncope.¹⁵

During outpatient follow-up 3 months after discharge, a pathological tilt test with cardioinhibitory response and syncope was recorded. About 6 months after discharge, the tilt test showed a normal cardiac response without syncope. These findings are consistent with a possible longstanding effect of the autonomous nervous system post-COVID-19.

In conclusion, although uncommon, syncope with prolonged asystole necessitating temporary pacing may be a rare presentation in patients with acute COVID-19. In cases with an overall benign course in terms of pulmonary involvement, a wait-and-see approach with regard to permanent pacing seems prudent. Also, a considerable time frame for the complete resolution of symptoms should be expected.

Lead author biography



Johannes Beil is a cardiology trainee with a subspecialty interest in pulmonary hypertension and interventional cardiology. He currently works at Unfallkrankenhaus Berlin but has also trained at University Hospital Munich and Hammersmith Hospital, London.

Supplementary material

[Supplementary material](#) is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and asso-

ciated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

References

1. Cha MH, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: a comprehensive review. *World J Gastroenterol* 2020;**26**: 2323–2332.
2. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. *Clin Neurol Neurosurg* 2020;**194**:105921.
3. Goldstein DS. The extended autonomic system, dyshomeostasis, and COVID-19. *Clin Auton Res* 2020;**30**:299–315.
4. Boccardi V. Autonomic dyshomeostasis in patients with diabetes mellitus during COVID-19. *Nat Rev Endocrinol* 2021;**17**:189.
5. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020;**17**:259–260.
6. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin Med (Lond)* 2021;**21**:e63–e67.
7. Goldstein DS. The possible association between COVID-19 and postural tachycardia syndrome. *Heart Rhythm* 2021;**18**:508–509.
8. Ebrille E, Lucciola MT, Amellone C, Ballocca F, Orlando F, Giammaria M. Syncope as the presenting symptom of COVID-19 infection. *HeartRhythm Case Rep* 2020;**6**:363–366.
9. Oates CP, Turagam MK, Musikantow D, Chu E, Shivamurthy P, Lampert J et al. Syncope and presyncope in patients with COVID-19. *Pacing Clin Electrophysiol* 2020;**43**:1139–1148.
10. Fudim M, Qadri YJ, Ghadimi K, MacLeod DB, Molinger J, Piccini JP et al. Implications for neuromodulation therapy to control inflammation and related organ dysfunction in COVID-19. *J Cardiovasc Transl Res* 2020;**13**: 894–899.
11. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest* 2007;**117**:289–296.
12. Leitzke M, Stefanovic D, Meyer JJ, Schimpf S, Schonknecht P. Autonomic balance determines the severity of COVID-19 courses. *Bioelectron Med* 2020;**6**:22.
13. Guilmot A, Maldonado Sloopjes S, Sellimi A, Bronchain M, Hanseeuw B, Belkhir L et al. Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. *J Neurol* 2021;**268**:751–757.
14. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A et al.; ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;**39**:1883–1948.
15. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM et al.; ESC Scientific Document Group. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–3520.