Received: 21 March 2021 | Revised: 24 May 2021 | Accepted: 27 June 2021

DOI: 10.1111/pace.14308

PACE WILEY

REVIEW

Bradyarrhythmias in patients with SARS-CoV-2 infection: A narrative review and a clinical report

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Abstract

Several cardiovascular diseases and arrhythmic disorders have been described in COVID-19 era as likely related to SARS-CoV-2 infection. The prognostic relevance of bradyarrhythmias during the infection has not been yet described and no data are available about long-term heart conduction disorders. A review of literature concerning the association between hypokinetic arrhythmias and COVID-19 from January 2020 to February 2021 was performed. The key-words used for the research were: "sinus node disfunction," "sick sinus syndrome (SSS)," "sino-atrial block," "atrio-ventricular block (AVB)," "bradyarrhythmias," and "COVID-19″ or "SARS-CoV-2." Excluding "relative bradycardia," a total of 38 cases of bradyarrhythmia related to SARS-CoV-2 infection have been described, even in very young people, requiring in many cases a definitive pacemaker implantation. Furthermore, we report a case of non-hospitalized 47-years old man with a SSS developed as a consequence of mild SARS-CoV-2 infection. While in all described cases heart conduction disorders were found at presentation of the infection or during hospitalization for COVID-19, in our case the diagnosis of SSS was made after the resolution of the infection. Although rarely, heart conduction disorders may occur during COVID-19 and the present case highlights that a cardiological follow up may be desirable even after the resolution of infection, especially in the presence of symptoms suggesting a possible heart involvement.

KEYWORDS
atrio-ventricular block, heart conduction disorders, SARS-CoV-2, sick sinus syndrome, sinus node dysfunction

1 | INTRODUCTION

Several cardiovascular diseases such as myocardial infarction, myocarditis, pulmonary embolism, vasculitis have been described in the Coronavirus Disease 2019 (COVID-19) era, probably related to the infection caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2).[1,2]

Among the mechanisms of cardiovascular damage, cardiac inflammation as well as the pro-thrombotic status and the high level of oxidative stress have been proposed,[3,4] mainly as a consequence of SARS-CoV-2 binding to Angiotensin-Converting-Enzime-2 (ACE-2) receptor and the excess of cytokines production, the so called "cytokine storm." This binding leads to an increased concentration of angiotensin II which exerts inflammatory and pro-thrombotic actions.[2,5] Furthermore, cardiac cell death might also be due to virus replication as well as to the increase of pro-inflammatory cytokines, fever, medications and hypoxemia.[6] The presence of a certain degree of sustained inflammation could also have consequences on cardiac function even after the resolution of the infection, as recently observed.[7] Although older age, male sex, thrombotic events, and hypoalbuminemia are

well-known risk factors for unfavorable outcomes during the course of SARS-CoV-2 infection, recently other arrhythmic disorders, including atrial fibrillation, have been recognized as additional markers of poor prognosis.[8,9] Ventricular arrhythmias have also been reported; however often related to drug-induced lengthening of the QT interval. In particular, hydroxychloroquine, which has been widely used in the first wave of the ongoing pandemic, has been reported to cause arrhythmic storms.[10] Less commonly, hypokinetic arrhythmias such as sick sinus syndrome (SSS), atrio-ventricular block (AVB) and bundle branch block (BBB) have been described.[11–13] However, their role as potential prognostic markers has not been defined yet, suggesting the need of additional investigations.[14] We performed a review of updated literature regarding the association between hypokinetic arrhythmias and SARS-CoV-2 infection and also we report the case of a SSS in a previously healthy young man developing after the resolution of a mild SARS-CoV-2 infection.

2 | METHODS

A review of current literature from January 2020 to February 2021 was performed. The studies were identified by searching electronic databases such as Pubmed and ScienceDirect. The key-words used for the research were: "sinus node disfunction," "SSS," "sino-atrial block," "AVB," "bradyarrhythmias," and "COVID-19" or "SARS-CoV-2." Only publications written in English and Italian languages were included in the literature research. Reference lists of all included studies were screened for potential additional studies. Data collected from each clinical case were: age, gender, respiratory failure at presentation or during hospitalization, time of worsening from clinical presentation, C-reactive protein (CRP) value, need for endotracheal intubation, type of conduction disorder and its reversibility, comorbidity, heart failure, need of permanent pacemaker, in-hospital follow-up. Results were expressed as median (range) or as mean (± standard deviation) for continuous variables, as appropriate, whereas for categorical variables number and percentages were used. In Table 1 are summarized all cases reported in scientific literature. In addition, we report a clinical case which focuses on the possibility of bradyarrhythmia onset early after mild infection of SARS-CoV-2.

2.1 | Case report

A 47-year-old man without relevant cardiovascular and medical history underwent cardiological consultation due to persistent fatigue. His recent history included SARS-CoV-2 infection, diagnosed after the occurrence of fever, headache, and dry cough. Since his clinical condition was good and stable, the patient did not require hospitalization and spent his quarantine at home, with disappearance of symptoms after 4 days. No medications, with the exception of paracetamol, were necessary. The patient turned negative for SARS-CoV-2 at nasopharyngeal swab 20 days after the first positivity.

Two months after recovery a cardiology consult was requested for fatigue. The patient was afebrile, heart rate 55 beats per min (bpm) with irregular pulse, respiratory rate 14/min, blood pressure 120/70 mmHg, oxygen saturation 98%. Physical examination and chest X-ray were normal. Blood examinations including serum troponin, CRP, D-Dimer, and thyroid function were normal. The 12-leads electrocardiogram (EKG) showed a sinus bradycardia with 55 bpm, narrow QRS, normal atrio-ventricular interval and sinus pauses of about 2 s. A 6-min walking test showed normal oxygenation and physiological increase of heart rate. An Holter EKG showed severe sinus arrhythmia with daytime bradycardia up to 30 bpm, junctional escape rhythm with atrio-ventricular dissociation and numerous electrical pauses with a maximum R-R interval of 2616 ms (Figure 1 a,b,c). The patient reported only fatigue and he had never experienced syncope. A cardiac magnetic resonance imaging was performed (Philips Achieva 1.5 T, cines, T2-weighted, perfusion and late gadolinium enhancement sequences; 0.1 mL/kg of gadobutrol 1.0 mmol/mL as contrast agent) and showed normal origin of coronary arteries, normal ejection fraction and the absence of myocardial edema or late gadolinium enhancement.

The patient underwent implantation of a loop recorder with remote monitoring. At 1-month follow-up, although the patient did not complain of symptoms, numerous electrical pauses, especially during nighttime, the longest of 4.2 s, were recorded (Figure 1 d,e). The patient is daily controlled by remote monitoring and follow-up is still ongoing in order to evaluate the indication to permanent pacemaker implantation.

3 | REVIEW OF THE LITERATURE

3.1 | Pathophysiology

The bradyarrhythmias observed in COVID-19 include SSS, sinus node disfunction, second and third degree AVB. Although not completely elucidated, the pathogenesis of bradyarrhythmias has been explained with several conditions occurring during SARS-CoV-2 infection, such as increased level of ACE-2,[15,16,31] direct injury of virus to cardiac cells,[6,20,29–33] hyperinflammatory status,[6,16,17,21,22,27,31] hypoxemia and electrolytic disorders,[19,21,29] imbalance of autonomic nervous system likely due to involvement of nervous system by virus infection[6,19] and side effect of medications.[24–26] A pivotal role is represented by the pro-inflammatory cytokine IL-6, which is the main responsible for cytokine storm during COVID and also is able to imbalance autonomic nervous system increasing vagal tone[36,37] (Figure 2). Among the included studies, an important insights on pathophysiology of bradyarrhythmias could be found in the article by *Goette* et al. were autopsy showed microangiopathy, myocardial necrosis, nerval ganglion cells with lymphocyte infiltration and viral alterations of right atrium, all conditions possibly implicated in bradyarrhythmias development.[6]

TABLE 1 Cases of heart block related to COVID-19 reported in literature

Case #	Age	Sex	Com.	Hosp.	C-RP (mg/dL)	RF	Day of clinical worsening (from first symptoms)	Endotracheal Intubation	Bradyarrhythmia	Day of bradyarrhythmia's presentation (from hospitalization)	BBB	AV interval (ms)	QRS interval (ms)	QRS morphology	Transience	HF	Pacemaker implantation	Exitus	Ref.
1	49	M	No	Yes	1.2	Yes	5	No	3° AVB	n.a.	No	n.a.	110	n.a.	Yes	No	No	No	15
2	58	M	No	Yes	n.a.	No	9	No	2:1 AVB	1	Yes	n.a.	130	LBBB	No	Yes	Yes	No	16
3	10	M	No	Yes	22	No	7	No	3° AVB	3	No	n.a.	110	n.a.	Yes	Yes	No	No	17
4	54	M	No	Yes	n.a.	Yes	13	No	3° AVB	14	Yes	n.a.	130	LBBB	Yes	No	No	No	18
5	82	M	S.	Yes	12	Yes	4	Yes	3° AVB	1	No	n.a.	110	n.a.	No	No	No	Yes	19
6	55	M	No	Yes	22	Yes	6	Yes	2° type 2 AVB	6	Yes	n.a.	130	RBBB	Yes	No	No	No	19
7	43	M	No	Yes	34	Yes	5	Yes	2° type 2 AVB	24	No	n.a.	110	n.a.	Yes	No	No	No	19
8	74	F	DM	Yes	n.a.	Yes	6	Yes	2° type 2 AVB	n.a.	Yes	n.a.	140	RBBB	No	No	No	Yes	20
9	71	M	No	Yes	3	Yes	3	No	3° AVB	3	Yes	n.a.	150	LBBB	NO	No	Yes	No	21
10	11	M	No	Yes	33	Yes	7	Yes	2° type 2 AVB	4	Yes	n.a.	130	LBBB	Yes	No	No	No	22
11	n.a.	n.a.	n.a.	Yes	n.a.	No	n.a.	n.a.	3° AVB	0	No	n.a.	n.a.	n.a.	No	n.a.	Yes	Yes	23
12	n.a.	n.a.	n.a.	Yes	n.a.	No	n.a.	n.a.	3° AVB	0	Yes	n.a.	n.a.	LBBB	No	n.a.	Yes	Yes	23
13	n.a.	n.a.	n.a.	Yes	n.a.	Yes	n.a.	n.a.	3° AVB	15	No	n.a.	n.a.	n.a.	Yes	n.a.	No	No	23
14	n.a.	n.a.	n.a.	Yes	n.a.	Yes	n.a.	n.a.	2° type 2 AVB	0	Yes	n.a.	n.a.	RBBB	Yes	n.a.	Yes	No	23
15	n.a.	n.a.	n.a.	Yes	n.a.	Yes	n.a.	n.a.	SSS	30	No	n.a.	n.a.	n.a.	No	n.a.	Yes	Yes	23
16	n.a.	n.a.	n.a.	Yes	n.a.	Yes	n.a.	n.a.	SSS	29	n.a.	n.a.	n.a.	n.a.	No	n.a.	Yes	Yes	23
17	n.a.	n.a.	n.a.	Yes	n.a.	Yes	n.a.	Yes	SSS	4	Yes	n.a.	n.a.	RBBB	No	n.a.	Yes	Yes	23
18	34	M	No	Yes	10	Yes	5	Yes	SSS	n.a.	No	200	110	n.a.	No	No	Yes	No	24
19	36	M	No	Yes	n.a.	No	n.a	No	SSS	n.a.	No	180	110	n.a.	No	No	Yes	No	25
20	67	M	No	Yes	54	Yes	6	Yes	Sinus arrest	6	No	200	110	n.a.	Yes	No	No	No	26

(Continues)

TABLE 1 (Continued)

Case #	Age	Sex	Com.	Hosp.	C-RP (mg/dL)	RF	Day of clinical worsening (from first symptoms)	Endotracheal Intubation	Bradyarrhythmia	Day of bradyarrhythmia's presentation (from hospitalization)	BBB	AV interval (ms)	QRS interval (ms)	QRS morphology	Transience	HF	Pacemaker implantation	Exitus	Ref.
21	54	F	No	Yes	6.3	Yes	n.a	No	3° AVB	n.a.	Yes	n.a.	120	RBBB	Yes	No	No	No	27
22	70	F	No	Yes	27	Yes	10	Yes	SSS	2	No	n.a.	110	n.a.	Yes	No	No	No	28
23	81	M	OSAS	Yes	13	Yes	7	Yes	SSS	4	No	n.a.	110	n.a.	Yes	No	No	No	28
24	76	M	DM	Yes	6,9	Yes	6	No	3° AVB	0	Yes	n.a.	130	RBBB	Yes	n.a.	No	No	29
25	82	M	No	Yes	n.a.	Yes	n.a.	n.a.	3° AVB	9	n.a.	n.a.	n.a.	n.a.	No	n.a.	Yes	No	29
26	69	F	H,DM,S	Yes	n.a.	Yes	6	No	2° type 2 AVB	8	No	n.a.	110	n.a.	Yes	No	No	No	30
27	83	F	H.	Yes	n.a.	No	8	No	SSS	8	No	160	110	n.a.	Yes	No	No	No	30
28	55	F	DM	Yes	5.7	No	n.a.	n.a.	3° AVB	n.a.	n.a.	n.a.	n.a.	n.a.	No	No	Yes	No	31
29	56	F	No	Yes	4.8	No	n.a.	n.a.	3° AVB	n.a.	n.a.	n.a.	n.a.	n.a.	No	No	Yes	No	31
30	67	M	H.,DM	Yes	8.1	No	n.a.	n.a.	3° AVB	n.a.	n.a.	n.a.	n.a.	n.a.	No	No	Yes	No	31
31	80	M	H.,M.I.	Yes	10.6	No	n.a.	n.a.	3° AVB	n.a.	n.a.	n.a.	n.a.	n.a.	No	No	Yes	No	31
32	45	F	No	Yes	39.5	No	n.a.	n.a.	SSS	n.a.	n.a.	n.a.	n.a.	n.a.	Yes	No	No	No	31
33	55	M	I.M.	Yes	7.4	No	n.a.	n.a.	3° AVB	n.a.	n.a.	n.a.	n.a.	n.a.	No	No	Yes	No	31
34	69	M	HF	Yes	n.a.	No	n.a.	n.a.	SSS	n.a.	n.a.	n.a.	n.a.	n.a.	Yes	Yes	No	No	31
35	53	M	No	Yes	5.7	No	4	No	2° type 2 AVB	3	No		110	n.a.	No	No	Yes	No	6
36	53	M	No	Yes	38	Yes	n.a.	Yes	SSS	3	n.a.	n.a.	n.a.	n.a.	No	No	Yes	Yes	32
37	75	F	No	Yes	11	Yes	n.a.	No	3° AVB	0	Yes		140	RBBB	No	No	Yes	Yes	33
38	71	F	DM	Yes	10.9	No	3	No	3° AVB	1	No	n.a.	110	n.a.	No	No	Yes	No	34
39[a]	47	M	No	No	n.a.	No	n.a.	No	SSS	60	No	160	110	n.a.	No	No	No	No	n.a.

Abbreviations: C-RP, C-reactive protein; Com, Comorbidities; Hosp., Hospitalization; RF, Respiratory failure at presentation; HCD, Heart conduction disorder; AVB, Atrio-ventricular block; RBBB, Right bundle branch block; LBBB, Left bundle branch block; SSS, Sick sinus syndrome; HF, Heart failure; M.I., Previous myocardial infarction; DM, Diabetes mellitus, S., Previous stroke; H., Hypertension; Ref, Bibliographic reference; n.a., Not applicable.
[a]Present case.

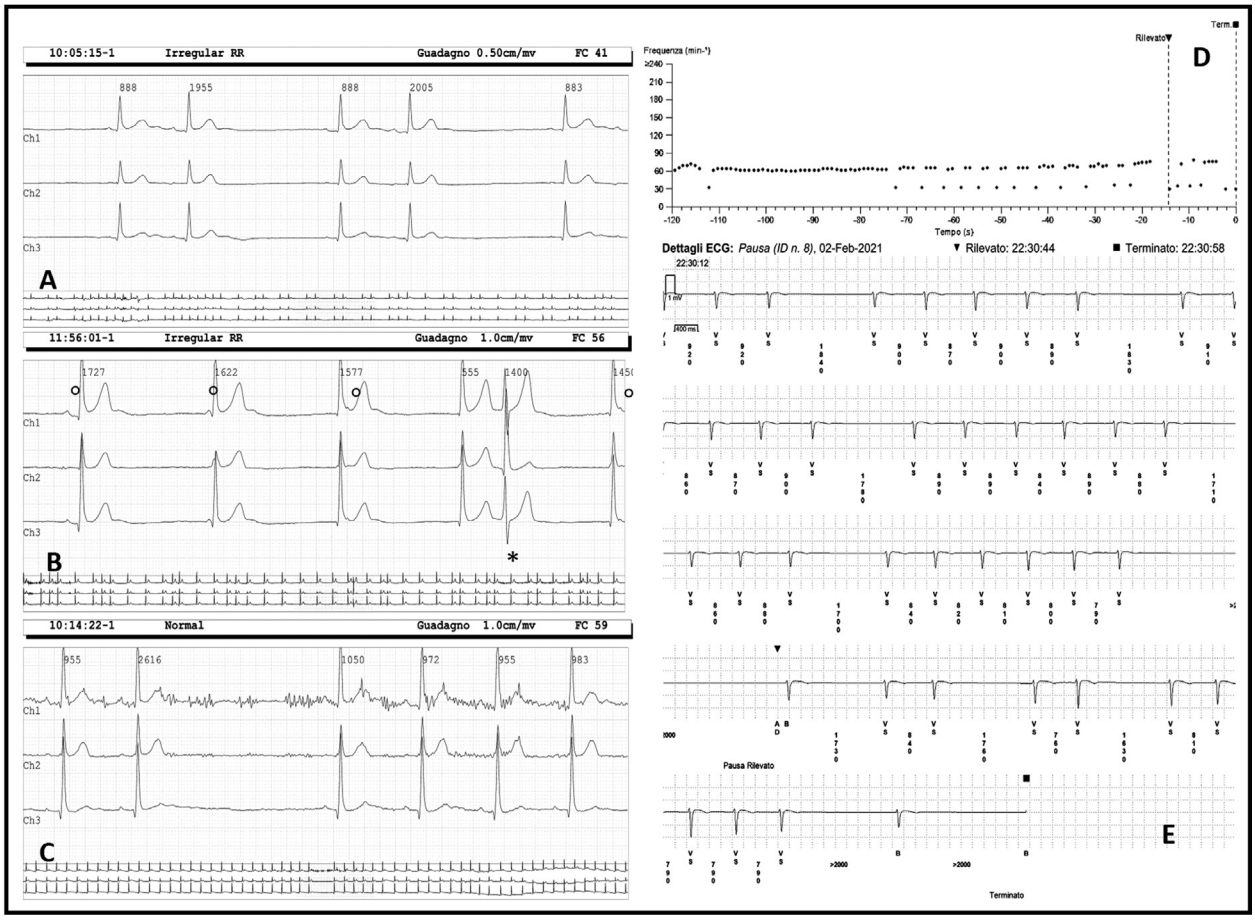

FIGURE 1 Holter EKG records: (A) sinus arrhythmia; (B) severe daytime bradycardia with atrioventricular isorhythmic dissociation and juntional escape rhythm, ° indicates dissociated P wave and * indicates an ectopic supraventricular early beat; (C) sinus pause of 2616 ms. Implanted Cardiac Monitor recording: (D) tachogram with revealed events; (E) sinus arrest, max R-R interval 4200 ms

3.2 | Assessment and diagnosis

A total of 38 cases, derived from 23 articles, of hypokinetic arrhythmias in patients with SARS-CoV-2 infection have been described so far (Table 1). Among the available data, mean age (±SD) of the patients was 59 ± 19 years old, with the youngest patient being 10 years old. Out of 31 patients, 21 (68%) were male, 10/31 (32%) female, in 7/38 (19%) this data were not available. In 31/38 (91%) medical history has been reported and cardiovascular risk factors such as diabetes, hypertension, obstructive sleep apnea or previous cardiovascular events were described in 11/31 (35%) of subjects. All the patients were hospitalized, with 23/38 (60%) developing severe respiratory failure. Worsening of clinical conditions occurred about 6 ± 2 days after first symptoms and 11/31 (35%) of patients required endotracheal intubation. CRP values at hospitalization was reported in 23/38 (61%) of cases and the mean value (±SD) was 18 ± 14 mg/dL. The most frequently reported bradyarrhythmias were second and third degree AVB in 26/38 (68%) patients and in 11/26 (42%) there was associated a BBB (46% left BBB, 54% right BBB). A marked bradycardia was described in all cases, in 12/38 (32%) of them sinus arrest or SSS were described, rarely associated with BBB (8%). The onset of cardiac conduction disorders was very variable, ranging from 0 to 30 days from hospitalization, with a median of 3.5 days. Although bradyarrhythmias are rarely described, relative bradycardia is a common characteristic in patients with SARS-CoV-2 infection.[38–42] The described bradyarrhythmias related to COVID-19 are summarized in Figure 3a and 3b.

3.3 | Treatment and prognosis

In 17/38 (44.7%) cases, the bradyarrhythmias were described as reversible, while in 20/38 (52.6%) patients pacemaker implantation was required (70% of patients with AVB and 30% of patients with SSS). When necessary, temporary pacemaker implantation was considered a reasonable option prior to implanting a permanent device due to the possible transient nature of bradyarrhythmias observed during COVID-19 and the risk of device infection.[13,23,37–39] The mean (±SD) age of patients who required definitive pacemaker implantation was 60 ± 18 years old, with the youngest patient being 34 years old. Nine out of 38 (23.6%) died during hospitalization due to refractory respiratory

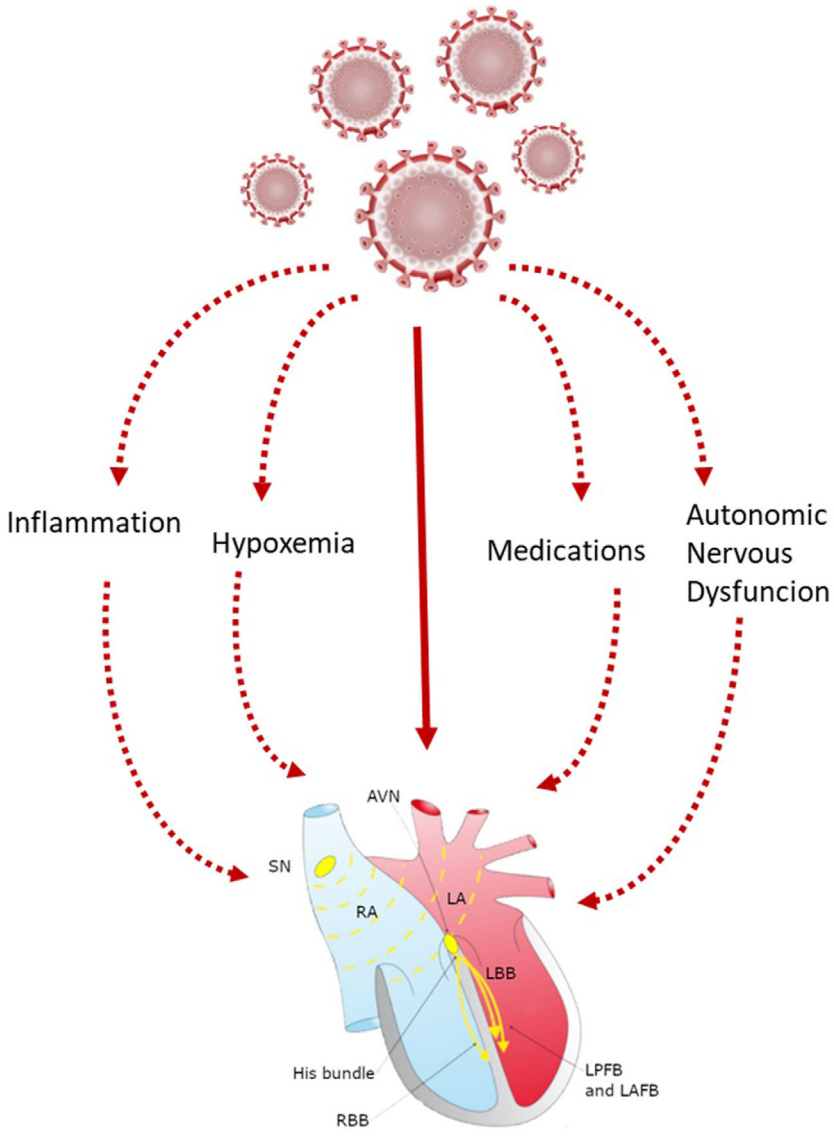

FIGURE 2 Proposed mechanisms of cardiac conduction system damage in SARS-COV-2 infection. ANS, autonomic nervous system; AVN, Atrio-ventricular node; SN, sinus node; RA, right atrium; LA, left atrium; RBB: right bundle branch; LBB, Left bundle branch; LPFB, left posterior fascicular bundle; LAFB, left anterior fascicular bundle [Color figure can be viewed at wileyonlinelibrary.com]

failure and 7/9 (77%) have had a definitive pacemaker implantation. Clinical studies addressing bradyarrhythmias and COVID-19 any are not available and major scientific evidences are based on case series. In the report by *Gupta* et al. two patients with SSS and five patients with atrioventricular block are described; in view of symptomatic bradyarrhythmias and the uncertainty of clinical course of COVID-19, the patients received emergent temporary transvenous pacing; all patients were strictly monitored for 10-14 days; 5/7 (71%) (mean age 62.6 ± 10.9 years old) with pacing dependent and symptomatic complete heart block underwent dual-chamber permanent pacemaker implantation, while 3/7 (29%) (mean age 57 ± 16.9 years old) with SSS were kept under medical follow-up.

In the report of *Chinitz* et al. 5/7 (71%) of patients undergone definitive pacemaker implantation and leadless pacemaker was chosen as best option due to lower probability of device infection; in 2/7 (28%) patients a temporary or semipermanent pacemaker was implanted.[23] In this population 4/7 (57%) of patients died and the patients with definitive pacemaker implantation were 4/5 (80%); *exitus* occurred between 1 and 32 days after the procedure (median 9.5 days). A recent study reported a low percentage (9/700, 1.2%) of bradyarrhythmias in hospitalized patient with COVID-19, and these seem not be related to acute mortality.[11] In the present report we described 38 patients with bradyarrhythmias and we found that *exitus* occurred in 23.6% (9/38) of patients, among these, 7/9 (78%) with definitive pacemaker.

The prognosis in patients with persistent bradyarrhythmias is not clearly defined, while some studies showed that clinical outcome (intensive care unit admission, intubation, death) was similar in patients with fever and relative bradycardia and in patients with fever and appropriate heart rate response.[41,42]

The percentage of pacemaker implantation in patients with heart conduction disorders and COVID-19, divided into those who survived and those who died, are reported in Figure 3c. Although not statistically significant, patients who did not survive to SARS-CoV-2 infection apparently more frequently had pacemaker implantation during hospitalization.

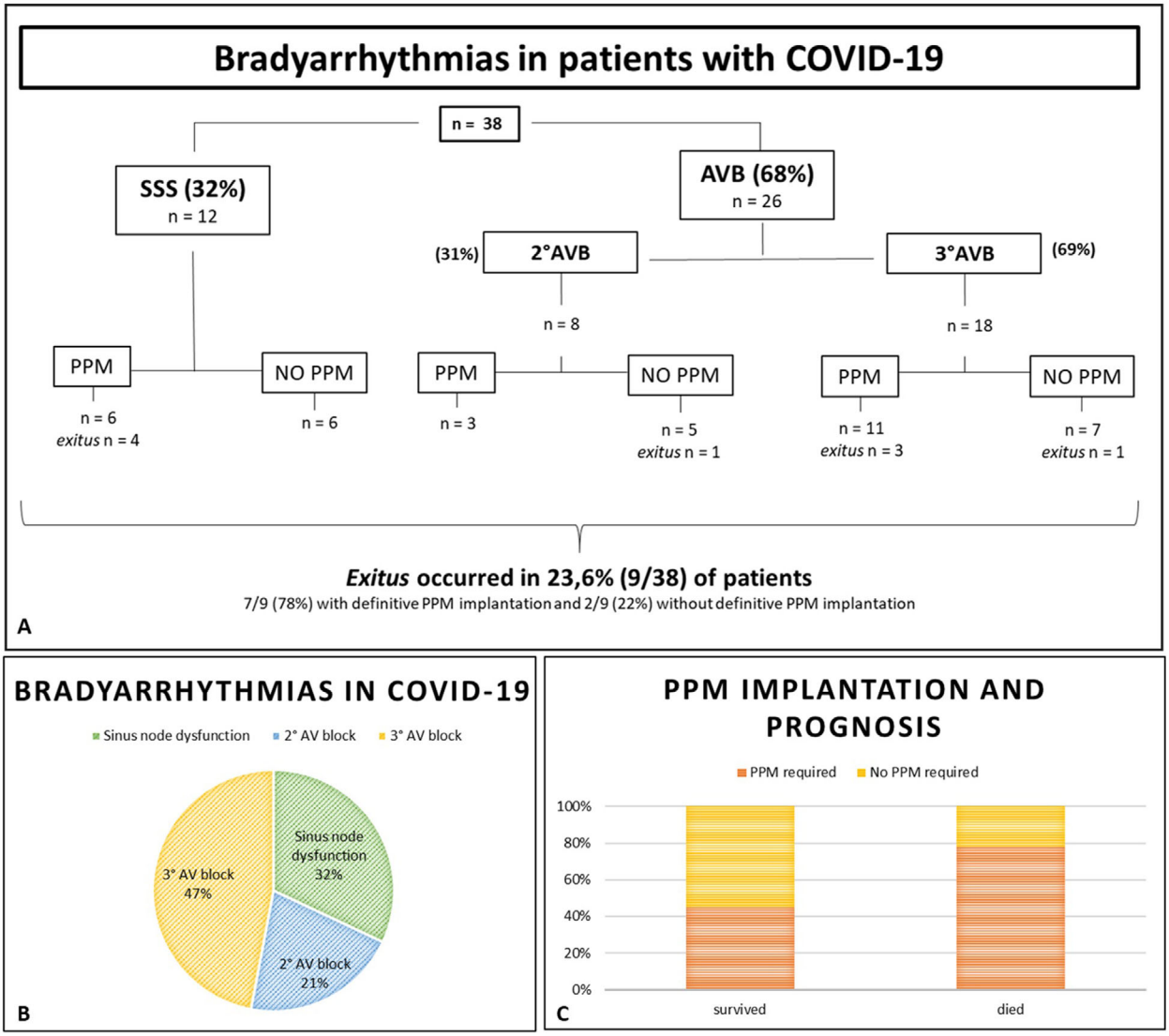

FIGURE 3 Bradyarrhythmias in patients with COVID-19 (A); percentage of heart conduction disorders (B); PPM implantation and prognosis (C); PPM, permanent pacemaker implantation; SSS, sick sinus syndrome; AVB, atrio-ventricular block [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Discussion and conclusions

Several cardiovascular diseases related to COVID-19 have been described so far, including, although rarely, bradyarrhythmias and heart conduction disorders such as bundle branch blocks, with the latter correlating with worse prognosis.[11–13] Moreover, the lack of the physiological heart rate increase during fever, named as "relative bradycardia," has been shown to represent an early sign of SARS-CoV-2 infection.[11,41] This condition had yet an acknowledged diagnostic significance in infectious diseases and has been associated also with typhoid fever, Legionnaire's disease, leptospirosis and certain viral infections.[43,44] Some years ago, relative bradycardia was described also during Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), more often related to medications as ribavirin and sometimes was related to poor prognosis.[45,46]

It now appears that patients with relative bradycardia should be monitored during the course of infection and follow-up. Nevertheless, all the bradyarrhythmias described so far occurred during hospitalization in the acute phase of the infection. To the best of our knowledge, we describe the first case of SSS diagnosed in an outpatient setting likely developed as a consequence of mild SARS-CoV-2 infection, since previous EKGs were normal and no causative conditions other than the recent SARS-CoV-2 infection were present.

Although severe SARS-CoV-2 disease affected many people worldwide and critically ill patients are usually ECG-monitored 24 h/d, only few cases of bradyarrhythmias have been described so far. It is likely that the onset of cardiac conduction disorders may have been underestimated and not correlated with COVID-19 only, since critical patients were mostly elder and with several comorbidities, conditions that may explain per se the occurrence of heart conduction disorders, while

cases of transient bradyarrhythmias may have not been judged clinically relevant and therefore may have not been reported. In addition, beyond relative bradycardia, which has been described to occur either at hospital admission and during hospitalization in patients with COVID-19,[41,42] apparently no other comprehensive study regarding cardiac conduction disorders during COVID-19 has been carried out so far and, currently, evidence is mostly provided by case reports.

From the available data in the literature, it is still unknown whether it is necessary to implant a permanent pacemaker and which would be the optimal timing of the procedure. Since we could not define with certainty the stability of the arrhythmic condition of our patient, and considering that he had never experienced syncope, we decided to implant a loop recorder with home monitoring in order to closely unveil the occurrence of severe bradyarrhythmias events which might subsequently require a definitive pacemaker implantation. The occurrence of heart conduction alterations following asymptomatic or mild COVID-19, as it happened in our case, should focus the attention towards possible late *sequelae* of SARS-COV-2 infection, suggesting that the virus itself should be considered an additional risk factor for cardiovascular disease.

The case herein presented highlights that cardiological evaluation during follow-up of outpatients with previous SARS-CoV-2 infection may be desirable, especially in the presence of symptoms suggesting a possible heart involvement. Although the proposal may seem unsustainable during a pandemic, it is also known that a not negligible rate of patients still experience symptoms (i.e., fatigue, pre-syncope, shortness of breath) even after SARS-CoV-2 infection resolution, and this is true not only for severe but also for mild infections, as it is the present case. Therefore, in order to screen for heart rhythm disorders a cardiological follow up may be reasonable in these patients.

In conclusion, heart conduction disorders may occur during the course of COVID-19 and, although less commonly, even after resolution of SARS-CoV-2 infection. The decision to pacemaker implantation should be based on accurate analysis aimed at evaluating the reversibility of this disorder, especially in young patients.

DATA AVAILABILITY STATEMENT

Data are available upon request from corresponding author.

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How to cite this article: Gatto MC, Persi A, Tung M, Masi R, Canitano S, Kol A. Bradyarrhythmias in patients with SARS-CoV-2 infection: A narrative review and a clinical report.. *Pacing Clin Electrophysiol*. 2021;44:1607–1615. https://doi.org/10.1111/pace.14308