2020

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Brief Communication

Brady-arrhythmias in Patients with COVID-19: Marker of Poor Prognosis?

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Verification: All authors had access to the data and a role in preparing the manuscript

Running Head: Brady-arrhythmias and prognosis in COVID-19

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Conflict of Interest Statement: The authors have no relevant conflicts of interest to disclose.
Funding Sources: None.

Key Words: COVID-19; Brady-arrhythmia; Temporary Pacing; Pacing strategies; Leadless pacemakers

Word Count: 1207

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pace.14042.

Abstract

Background: Despite descriptions of various cardiovascular manifestations in patients with COVID-19, there is a paucity of reports of new onset brady-arrhythmias, and the clinical implications of these events are unknown.

Methods: Seven patients presented with or developed severe brady-arrhythmias requiring pacing support during the course of their COVID-19 illness over a six-week period of peak COVID-19 incidence. A retrospective review of their presentations and clinical course was performed.

Results: Symptomatic high degree heart block was present on initial presentation in 3 of 7 patients (43%), and 4 patients developed sinus arrest or paroxysmal high degree AV block. No patients in this series demonstrated left ventricular systolic dysfunction or acute cardiac injury, whereas all patients had elevated inflammatory markers. In some patients, brady-arrhythmias occurred prior to the onset of respiratory symptoms. Death from complications of COVID-19 infection occurred in 57% (4/7) during the initial hospitalization, and in 71% (5/7) within three months of presentation.

Conclusions: Despite management of bradycardia with temporary (3/7) or permanent leadless pacemakers (4/7), there was a high rate of short-term morbidity and death due to complications of COVID-19. The association between new-onset brady-arrhythmias and poor outcomes may influence management strategies for acutely ill patients with COVID-19.

Introduction

Various cardiovascular complications have been described in patients with Coronavirus 2019 (COVID-19), and with it a concern for a higher mortality.[1] Recent reports have described acute cardiac injury,[2,3] cardiogenic shock,[3] electrocardiographic (ECG) changes,[1,4] right ventricular dysfunction,[5] thromboembolic complications,[6] and tachy-arrhythmias.[7] Ventricular arrhythmias have been reported as the first clinical manifestation of COVID-19.[8] However, reports of severe brady-arrhythmias have been rare, mostly anecdotal, and likely under-reported.[9] The clinical implications of new onset brady-arrhythmias in patients with COVID-19 are unknown, and the approach to management is debatable without understanding short- and long-term outcomes, and the risk to health care providers involved with urgent invasive procedures.

Herein we report 7 cases of patients admitted to our health system in Suffolk County, New York during the initial six-week period of peak COVID-19 incidence, who presented with or developed severe brady-arrhythmias during hospitalization. The management strategies and short-term outcomes including in-hospital mortality are described.

Methods

We included all patients with confirmed COVID-19 admitted March 15 - April 30, 2020, to two affiliated hospitals who required pacing support for severe bradycardia. Patients were excluded if their bradycardia required only medication adjustment, was identified only at the time of death, or if an alternate etiology of bradycardia was suspected. Clinical data was obtained from the electronic medical record. All testing and treatment, including

permanent and temporary pacemaker implantations, were performed at the discretion of the treating physicians.

The Northwell Health Institutional Review Board approved this case series as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent. The initial characteristics of 5700 patients from Northwell are presented elsewhere;[2] this case series presents in-depth cardiac results not in that article.

Results

Between March 15 and April 30, 2020, seven patients with confirmed COVID-19 and severe bradycardia requiring acute intervention were retrospectively identified. Demographic and clinical characteristics of these patients are shown in **Table 1**. An overview of each patient's presentation and clinical course are presented in **Table 2**.

Symptomatic high degree heart block was present on initial presentation in 3 of 7 patients (43%); in two patients, respiratory symptoms developed later in their hospitalization (despite chest radiography suggestive of viral pneumonia at presentation) and the diagnosis of COVID-19 was made after permanent pacemaker implantation (**Figure 1**). Four patients developed sinus arrest or paroxysmal high degree atrioventricular (AV) block lasting between 10-37 seconds documented on inpatient telemetry.

No patients in this series had preexisting cardiac disease. No significant QT prolongation was noted at baseline or during hospitalizations, though preexisting conduction disease was present in 3 patients. Echocardiography performed during hospitalization, or within 6 months prior, revealed normal left ventricular systolic function in all patients (left ventricular ejection fraction 67.5% ±14.3%). Severe pulmonary hypertension and/or right

ventricular dysfunction was identified in two patients. There was no evidence of acute coronary syndrome or documented thromboembolism. Respiratory symptoms and radiographic evidence of viral pneumonia were ultimately present in all patients.

Laboratory findings demonstrated significantly elevated inflammatory markers in all patients. No significant electrolyte or thyroid function abnormalities were observed. Cardiac troponin levels (measured with the Roche troponin T assay) were normal in three patients (≤0.01 ng/mL), not measured in two patients, and mildly elevated in two patients who both had concomitant renal insufficiency: patient #1 had ESRD and peak troponin 0.23 ng/mL, and patient #5 had a peak troponin of 0.17 ng/mL in the setting of acute renal failure and peak creatinine >6 mg/dl) (Table 1). No patients demonstrated ischemic ECG changes apart from bradycardia or conduction disturbances. Two patients received new rate-slowing medication prior to the brady-arrhythmia events, however, this was not considered to be the primary factor precipitating bradycardia in either case. Five patients received hydroxychloroquine during their hospitalization, four prior to their first recorded bradycardia episode.

Due to perceived life-threatening bradycardia, all patients received temporary (3/7) or permanent pacemakers (4/7). One patient (patient #5) who received a temporary pacemaker after the initial bradycardia event subsequently received a leadless pacemaker due to recurrent bradycardia. In all five patients receiving permanent pacemakers, a leadless pacemaker (Medtronic Micra®) was implanted. No operating staff involved in these procedures subsequently developed COVID-19.

Mortality in this cohort was high, as 5/7 (71%) patients died within three months following admission. Four of the seven patients (57%) died during the initial hospitalization, occurring 17.3 +/- 12.5 days following admission and 8.3 +/- 10.7 days after the first

identified brady-arrhythmia. All mortalities were considered complications of COVID-19 infection, including three patients with hypoxemic respiratory failure, and one who developed fevers, lethargy and hypoglycemia prior to expiration, presumed to be due to COVID-19 sepsis. Another patient had a prolonged hospital course with multisystem organ failure ultimately requiring tracheostomy and feeding tube placement, and suffered further complications following discharge to a long-term care facility prompting withdrawal of supportive care and subsequent expiration on day 90 following initial hospital admission. In the two patients who survived, one had an acute stroke and the other had transient severe encephalopathy during their hospitalizations.

Discussion

In this series of 7 patients with COVID-19 and severe brady-arrhythmias, short-term mortality and morbidity was high, despite prompt management of bradycardia with pacing support. All patients had elevation of inflammatory markers and multisystem organ involvement, without acute cardiac injury or associated cardiomyopathy. In some patients, brady-arrhythmias presented prior to the onset of respiratory symptoms.

The mechanism of cardiac involvement during COVID-19 remains speculative. Acute bradycardia may be due to direct SARS-CoV-2 infiltration of myocardial cells and the dedicated conduction system, aggravation of pre-existing conduction disease during acute illness, pulmonary injury leading to hypoxia and secondary bradycardia, or collateral damage from inflammatory system activation and cytokine storm.[10] SARS-CoV-2 may also activate the ACE2 receptor,[10] as ACE2 expression has been demonstrated specifically in sino-atrial nodal cells,[11] and ACE2 overexpression has been associated with conduction disturbances.[12]

In addition, the SARS-CoV virus causing the 2002 outbreak was associated with sinus bradycardia in up to 15% of patients.[10,13]

Adverse effects of medications, including chloroquine and hydroxychloroquine, may also contribute to conduction system dysfunction. Long-term chloroquine use has been shown to increase Purkinje fiber refractory period and action potential duration, resulting in AV nodal and infra-Hisian conduction disturbance,[14] most commonly fascicular block.[15] Five patients in this series were treated with hydroxychloroquine, though this treatment preceded the development of bradycardia in only four.

All patients received temporary or permanent pacing. A leadless pacemaker was implanted in all patients clinically deemed to require permanent pacing. Leadless pacemaker implantation may be an attractive option in patients with active COVID-19, as the risk of cardiac and intravascular infection may be lower, and the risk of viral transmission to operating staff may be mitigated by the percutaneous approach. However, despite pacing support, outcomes were poor, with 4/7 patients dying during initial hospitalization, and 5/7 dying within three months due to complications of COVID-19.

Conclusion

Brady-arrhythmias may occur as part of the clinical course in patients with COVID-19. In our experience, acute bradycardia was associated with elevation of inflammatory markers and high short-term mortality rates, despite lack of co-existent cardiomyopathy or acute cardiac injury. Management decisions and resource allocation should take into account the potential for adverse outcomes regardless of invasive pacing support, as well as potential risks to health care staff during intervention on these acutely ill patients.

Acknowledgement

We would like to acknowledge the contributions of the Northwell Health COVID-19 Research Consortium.

Author contributions

Concept/design: JC, RG, LE, LG, PG

Data analysis/interpretation: JC, MH, LG, PG

Drafting article: JC, MH, RG,

Critical revision of article: LG, PG, LE, LO

Approval of article: all authors

Statistics: JC, MH

Data collection: JC, RG, GV, RJ, PM, LE

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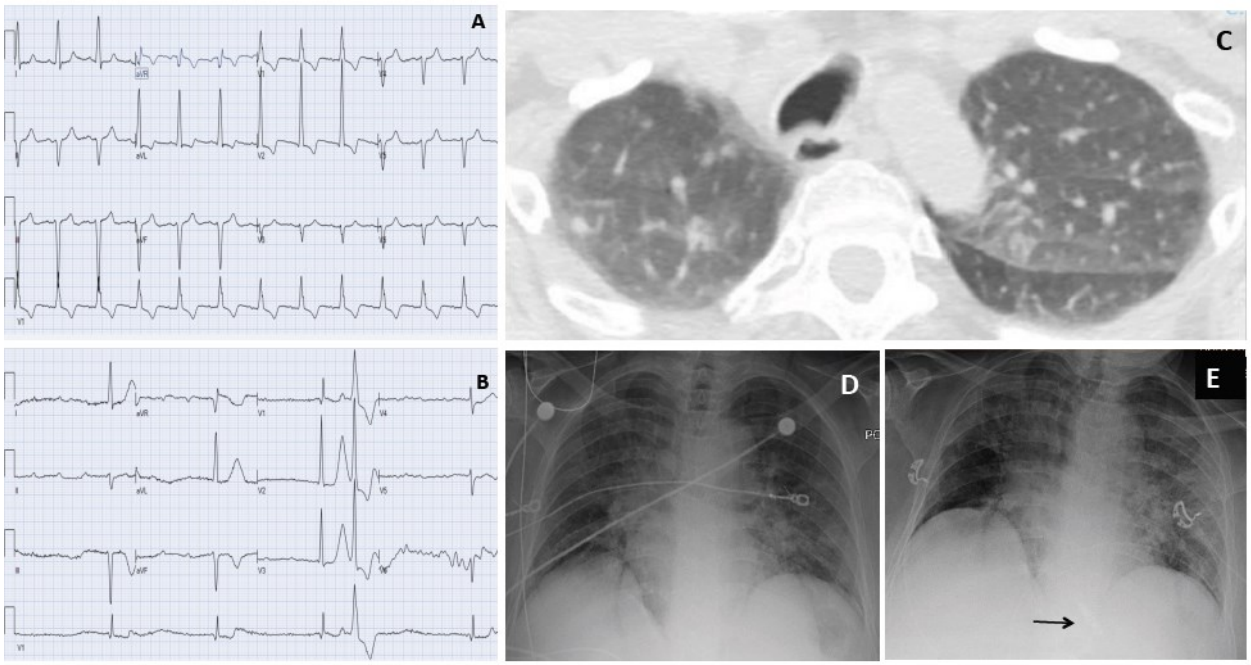
Figure Legend

Figure 1. **A patient presenting with AV block and imaging findings consistent with COVID-19 prior to development of pulmonary symptoms.**



A: Baseline ECG prior to admission. **B**: ECG on presentation demonstrating 3rd degree AV block. **C**: CT on admission with incidental findings of ground-glass nodular opacities in the lung apices. **D** and **E**: Chest X-ray from admission, and following leadless pacemaker implant (arrow) showing progressive bilateral pulmonary infiltrates.

Table 1. Clinical Characteristics on Presentation

Parameter	**Overall (n=7)**
a) **DEMOGRAPHICS**	
b) Age (years)	64 ± 9.6
Male gender	42.9% (3)
Residential Care Facility Resident	28.6% (2)
Obese (BMI>30)	28.6% (2)
CARDIOVASCULAR RISK FACTORS	
Hypertension	71.4% (5)
Hypercholesterolemia	14.3% (1)
Diabetes Mellitus	85.7% (6)
Hepatic disease/Cirrhosis	28.6% (2)
Cerebrovascular Disease / Stroke prior to admission	14.3% (1)
Chronic Kidney Disease	14.3% (1)

BASELINE CONDUCTION DISEASE	
RBBB	28.6% (2)
LBBB	0% (0)
LAHB + RBBB	14.3% (1)
First degree AVB	14.3% (1)
Prior Sinus Node Dysfunction	0% (0)
SYMPTOMS ON HOSPITAL PRESENTATION	
Dyspnea	57.2% (4)
c) Fever	57.2% (4)
d) Chest Pain	28.6% (2)
e) Dizziness	42.9% (3)
MEDICATIONS	
Beta-blocker	28.6% (2)
ACE-Inhibitor or Angiotensin Receptor Blocker	14.3% (1)
Aspirin	28.6% (2)
Hydroxychloroquine	71.4% (5)
Actemra	28.6% (2)
Anakinra	14.3% (1)
Convalescent Plasma	14.3% (1)
LABORATORY VALUES	
Troponin (n=5)	
Initial	0.046±0.103
Peak	0.08±0.112
CRP (n=6)	
Initial	15.3±16.1
Peak	22±13.8

Ferritin (n=5)	
Initial	1109±337
Peak	5017±6955
D-dimer (n=5)	
Initial	2938±4085
Peak	7636±6986
AST	
Initial	51±31
Peak	971±2276
ALT	
Initial	31±9
Peak	540±1189
Potassium	
Initial	4.6±0.8
Minimum	3.6±0.9
Peak	5.2±1.1
Magnesium	
Initial	2.1±0.4
Minimum	1.9±0.5
Peak	2.6±0.6

Table 2. Patient Specific Clinical Events and Outcomes

Patient	Presenting Symptoms/ Diagnosis	Bradycardia Present on Admission	Preexisting Conduction Disorder	COVID-19 Symptoms (non-cardiac)	Bradycardia Event (# of Days After Admission)	Intervention (# of Days after Admission)	Outcome at End of Hospitalization (# of Days after Admission)
***f)* #1**	Dizziness, weakness, acute CVA	CHB	1st degree AV block	Brief dyspnea with pulmonary infiltrates found on CXR day 21 of hospitalization	CHB with narrow complex escape rhythm (0)	Leadless pacemaker implant (2)	Death (26)
***g)* #2**	Fall	CHB	RBBB, LAFB	Fever and hypoxia starting day 2 of hospitalization	CHB with wide complex escape rhythm (0)	Leadless pacemaker implant (0)	Death (6)
#3	Unilateral facial droop, abdominal pain	None	Leftward axis only	Fever, cough starting day 1 of hospitalization	Sinus bradycardia and intermittent CHB with junctional escape rhythm (15)	Temporary pacemaker (26)	Discharged (40) *No permanent pacing required*
#4	Dizziness, fever, dyspnea, pleuritic chest pain	2:1 AV block	RBBB	Fever, chills, cough, dyspnea and pleuritic chest pain on presentation	2:1 AV block (0)	Leadless pacemaker implant (2)	Discharged (15) *No permanent pacing required*
#5	Myalgias, cough, dyspnea and pleuritic chest pain	None	None	Myalgias, cough, dyspnea, pleuritic chest pain	Sinus pauses up to 10 seconds (30)	Semi-permanent pacemaker implant (34) and leadless pacemaker implant (58)	Discharged to long-term acute care facility (48) Death due to further complications (90)

#6	Myalgias, cough, dyspnea, fever, anorexia	None	None	Myalgias, cough, dyspnea, fever, anorexia on presentation	Sinus pauses up to 17 seconds and sinus arrest requiring rescucitation (29)	Semi-permanent pacemaker implant (29)	Death (30)
#7	hypoxemic respiratory failure, ARDS, encephalopathy, unresponsiveness	None	None	Hypoxemic respiratory failure, ARDS, encephalopathy, unresponsiveness on presentation	Sinus pause of 36 seconds and new RBBB with right axis deviation (4)	Leadless pacemaker implant (5)	Death (7)