Sinus bradycardia is associated with poor outcome in critically ill patients with COVID-19 due to the B.1.1.7 Lineage

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\textbf{ABSTRACT}

The progress of COVID-19 from moderate to severe may be precipitous, while the characteristics of the disease are heterogeneous. The aim of this study was to describe the development of sinus bradycardia in critically ill patients with COVID-19 and its association with outcome in outbreak due to the SARS-CoV-2 B.1.1.7 Lineage. We leveraged the multi-center SuPAR in Adult Patients With COVID-19 (SPARCOL) study and identified patients who required admission to intensive care unit (ICU). Inclusion criteria were: (a) adult (≥18 years old) patients hospitalized primarily for COVID-19; (b) a confirmed SARS-CoV-2 infection diagnosed through reverse transcriptase polymerase chain reaction test of nasopharyngeal or oropharyngeal samples; and (c) at least one blood sample collected at admission and stored for suPAR, hs-CRP, and ferritin testing. All patients had continuous heart rate monitoring during hospitalization. In total, 81 patients were included. Of them, 17 (21 %) and 64 (79 %) were intubated and admitted to the ICU during the first and second wave, respectively. Two (12 %) and 62 (97 %) developed bradycardia before ICU admission, respectively (p < 0.001). Patients with bradycardia had increased suPAR (p < 0.001) and hs-CRP level (p < 0.001). Infusion of isoprenaline and/or noradrenaline was necessary to maintain an adequate rate and peripheral perfusion in all patients. Mortality was significantly higher in patients with bradycardia (p < 0.001). In conclusion, bradycardia was associated with poor outcome. As B.1.1.7 variant strain is spreading more rapidly in many countries, our findings help in the identification of patients who may require early admission to ICU.

1. Introduction

Coronavirus outbreaks are a global public health threat due to their high capacity for mutation and recombination \cite{1}. Although several months have been passed after the inception of the SARS-CoV-2 pandemic, the numbers of critically ill patients with severe coronavirus disease 2019 (COVID-19) are increasing in many European countries. COVID-19 is a lower respiratory tract infection, but arrhythmias and other cardiovascular symptoms are frequently reported. Cardiac arrhythmias may contribute to morbidity and mortality and have been observed in up to 44.4 % of COVID-19 patients, depending on the

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severity of the disease [2,3]. In a recent study of 113 COVID-19 patients requiring intensive care unit (ICU) treatment, 50 episodes of sustained atrial tachycardias, 5 episodes of sustained ventricular arrhythmias, and 30 bradicardic events were documented [4]. Only 5 bradicardic events were associated with hemodynamic deterioration; however, whether bradycardia is associated with worse outcomes remains unknown.

A new variant of SARS-CoV-2 was first detected in the United Kingdom in September 2020. This variant, called B.1.1.7, is known to spread more easily and may be more deadly than previous variants. To date, the new variant has spread to more than 90 countries worldwide, and further diagnostic measures are needed to prevent additional mortality [5]. In a recent genetic analysis in Greece, the B.1.1.7/UK lineage (Variant VOC_202012) was reported in 88.4 % of the samples, while in a previous analysis the same variant was reported in only 1.3 % of the samples [6]. On the contrary, the main variants during the first wave (March - July 2020) were the B.1.1, B.1, and B.1.1.74. Since December 2020, the British variant has become widespread also in Spain, constituting around 15–20 % of the cases [7]. The aim of this study was to describe the development of sinus bradycardia in critically ill patients with COVID-19 and its association with outcome in outbreak due to the SARS-CoV-2 B.1.1.7 Lineage.

2. Materials and methods

2.1. The SuPAR in adult patients with COVID-19 study

We leveraged the SuPAR in Adult Patients With COVID-19 (SPARCOL) study (ClinicalTrials.gov Identifier: NCT04590794) and included consecutive patients requiring ICU admission. The primary aim of the study was to estimate the incidence of sinus bradycardia (sustained sinus rhythm with a resting heart rate ≤60 bpm, diagnosed and monitored with continuous heart rate monitoring) and its clinical implications in patients with COVID-19.

The Institutional Review Board of the University Hospital of Larisa approved the study (IRB no. 17543). The study was performed according to national and international guidelines and consent procedures were obtained. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for observational cohort studies [8].

2.2. Study design and outcomes definitions

We collected data from 252 COVID-19 patients during the period of April 1st to December 31st, 2020, the date the database was locked for the purpose of this analysis. Also, we divided the study period into two consecutive cohorts according to the duration of the two COVID-19 waves in most European countries (April 2020 - July 2020 and August 2020 - December 2020).

In order to decrease the effects of comorbidities and the associated medication on cardiac rhythm and rate, we excluded from this analysis patients with confirmed SARS-CoV-2 infection who were not primarily admitted for COVID-19, patients with incomplete data, patients with pre-existing severe cardiac or respiratory disease, such as heart failure, more than mild chronic obstructive pulmonary disease or pulmonary vascular disease, patients with pacemaker/implantable cardioverter-defibrillator, and patients who were intubated due to cardiac arrest.

2.3. Statistical analysis

Statistical analysis was performed using R v4.0. Differences between numerical observations in the first and second wave were detected using the non-parametric Mann-Whitney test. The chi-square test of independence was applied to the categorical observations, while in both cases, the Benjamini-Hochberg false discovery rate correction was applied to account for the multiple number of tests. In this study, adjusted p-values less than 0.05 were deemed significant. For linear correlation we used Spearman’s rho coefficient. A logistic regression model was fitted with the presence of bradycardia as the dependent factor and wave and the different probable confounding factors as independent variables. A log-likelihood test was used to assess the significance of each term. The respective odds ratio and p-value was computed for each variable, while no adjustment was applied in the resulting p-values from this model.

3. Results

In total, 252 consecutive patients were hospitalized for COVID-19 and 81 (32 %) required intubation and ICU admission (first wave 17 (21 %); second wave 64 (79 %)). Of them, two (12 %) and 62 (97 %) patients from the first and second wave, respectively, developed sinus bradycardia before ICU admission (Table 1, Fig. 1). In the second wave, the average time for development of bradycardia was 5 and 10 days from admission and onset of symptoms, respectively. All patients developed bradycardia without clinically detectable myocardial necrosis and none of them was receiving drugs inducing bradycardia, such as hydroxychloroquine, moxifloxacin, azithromycin, or remdesivir. There were no statistically significant differences in comorbidities or prior medication between patients with and without bradycardia. In all patients with bradycardia, infusion of isoprenaline and/or noradrenaline was necessary to maintain an adequate rate and peripheral perfusion before intubation and especially during ICU stay. In both waves, the dose of isoprenaline and norepinephrine increased during ICU stay, with patients of the second wave requiring higher infusion rates (p < 0.001) (Fig. 2).

Mortality was higher in patients with bradycardia (64 % vs. 11 %, p < 0.001) (Table 1). The median survival time of the study cohort was 20 days (95 % CI: 17 - 23 days).

Table 1

| Clinical and laboratory characteristics at ICU admission and outcome (N = 81). | Without bradycardia | With bradycardia | Adjusted p-value |
|--------------------------------------------------------------------------|---------------------|-----------------|-----------------|
| Age (years), mean (SD)                                                   | 66.2 (12.6)         | 69.1 (10.8)     | 0.071           |
| Wave                                                                     | First, n (%)        | 15 (19)         | 2 (2)           | <0.001         |
|                                                                            | Second, n (%)       | 2 (2)           | 62 (77)         |               |
| Sex - Male, n (%)                                                        | 9 (11)              | 44 (54)         | 0.019           |
| Smoking - Yes, n (%)                                                     | 7 (9)               | 18 (22)         | 0.05            |
| APACHE II, mean (SD)                                                     | 10.86 (4.7)         | 17.36 (4)       | <0.001          |
| SOFA, mean (SD)                                                          | 10.73 (2.5)         | 12.63 (2.2)     | <0.001          |
| Heart rate (beats per minute), mean (SD)                                | 73.3 (67.6)         | 55.2 (67.3)     | <0.001          |
| Prior use of b-blocker                                                  | –                   | 51.3 (6.13)     |                 |
| Mean arterial pressure (mmHg), mean (SD)                                 | 87.28 (10.1)        | 81.28 (12.1)    | <0.001          |
| PaO2/FiO2 ratio, mean (SD)                                               | 204.24 (78.4)       | 128.75 (56.9)   | <0.001          |
| pH, mean (SD)                                                            | 7.36 (0.1)          | 7.28 (0.1)      | <0.001          |
| Temperature (°C), mean (SD)                                              | 37.91 (0.8)         | 38.44 (1)       | <0.001          |
| Hemoglobin (g/dL), mean (SD)                                             | 10.97 (1.9)         | 11.39 (9.1)     | 0.297           |
| White blood cells (K/µL), mean (SD)                                      | 9.52 (4.9)          | 10.29 (5.2)     | 0.118           |
| High-sensitivity CRP (mg/L), mean (SD)                                   | 3.2 (4.7)           | 13.27 (23.1)    | <0.001          |
| D-Dimers (ng/mL), mean (SD)                                              | 10,203.5 (1259.9)   | 1369.94 (1238.4)| <0.001          |
| Ferritin (ng/mL), mean (SD)                                              | 3970.3              | 2628.32 (4638.3)| 0.011           |
| suPAR (ng/mL), mean (SD)*                                                | 7.65 (5.2)          | 9.07 (4.3)      | <0.001          |
| Lactate (mmol/L), mean (SD)                                              | 2.09 (1.5)          | 4.96 (3.6)      | <0.001          |
| Death, n (%)                                                            | 9 (11)              | 52 (64)         |                 |
| Outcome Hospital discharge, n (%)                                        | 10 (12)             | 10 (12)         | <0.001          |

ICU, intensive care unit; CRP, C-reactive protein.

* Six patients of the second wave were on chronic antihypertensive treatment with b-blockers (bisoprolol, n = 2; nebivolol, n = 4), but all of them received the last dose more than 48 h before admission.

* Measured at hospital admission.
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respiratory or other types of infection, preexisting arrhythmia, or car
SARS-CoV-2 B.1.1.7 Lineage.

duction system and considering the high mortality worldwide, we

piratory function, serum biomarkers of inflammation, and myocardial

now, patient characteristics, baseline electrocardiogram features, res
bradycardia developed without clinically detectable myocardial necro

The most important finding in this study was the association between
the development of bradycardia and poor outcome. In our patients,

< 0.001). After adjusting for different confounding factors (age, sex) and
different comorbidities, such as COPD, diabetes mellitus, kidney injury,
respiratory or other types of infection, preexisting arrhythmia, or car-
diovascular comorbidities, only the onset of bradycardia was associated
with mortality (p < 0.001). All survivors had bradycardia at ICU
discharge.

4. Discussion

The most important finding in this study was the association between
the development of bradycardia and poor outcome. In our patients,

December, 2020. Patients infected with the B.1.1.7 variant seem to be
younger, with fewer comorbidities, but with an increased risk of hos-
pitalization per case associated with B.1.1.7 on a population level [12].
In our patients, the average time for development of bradycardia was
significantly shorter compared to other cohorts, but similar to the UK
cohort [9,10].

The underlying pathophysiology and pathogenesis of bradycardia is
complex and several mechanisms may be implicated in its development.
in our cohort, suPAR and hs-CRP were significantly higher in patients
with bradycardia. suPAR level ≥ 6 ng/mL has been independently
associated with the development of organ failure in patients with
COVID-19 [13–15], and therefore, bradycardia may be associated with
the severity of inflammation and disease progression. In addition,
proinflammatory cytokines released upon pulmonary infection activate
vagal afferent and subsequent vagal efferent signaling [16]. The latter
are a main component of the cholinergic anti-inflammatory pathway
that modulates the inflammatory response through interaction with
peripheral α7 subunit-containing nicotinic acetylcholine receptors
(nAChRs) [17]. Animal studies have shown that it is possible to activate
the cholinergic anti-inflammatory pathway by delivering an electrical
charge that is below the threshold required to significantly change heart
rate because the neural tracts descending in the vagus nerve to modulate
immune responses function at a lower firing threshold than the
cardio-inhibitory fibers [18,19]. Therefore, the initial activation of the
cholinergic anti-inflammatory pathway may not affect chronotropy, but
excessive pathway activity may increase heart rate because the activa-
tion of α7 nAChRs elicits a sympathetic cardiovascular response [20,21].
Moreover, SARS-CoV-2-induced neuronal cell death paupersizes
angiotensin-converting enzyme 2 receptors in the cardiovascular loci of
central nervous system leading to prolonged activation of the sympa-
thetic system with concomitant reduced vagal activity [22]. When vagus
nerve activity is deficient, inflammation is excessive [19], which may
explain the higher ferritin levels in the non-bradycardic group.

The lower (but still higher than normal) ferritin levels in the bra-
dycardic patients, together with the increased levels of suPAR and hs-
CRP, may reflect a more severe disease and a heightened activity of
the cholinergic anti-inflammatory pathway. However, the onset of
bradycardia in our patients may imply an increased and amplified
binding of SARS-CoV-2 Spike glycoproteins to the α7nAChRs, which
prevents the immunosuppressive effects of acetylcholine and decreases
heart rate [23,24], as well increased vagal activity. In addition, the
absence of myocardial necrosis together with the increase in D-Dimer
may indicate other uncharacterized pathways of electrical conduction
defects. An increase in blood pressure in patients with COVID-19, caused
by the severe inflammatory response and/or in an effort to maintain
tissue oxygenation, may lead to turbulent microcirculatory blood flow.
The resulting higher or lower (than physiological) shear stress impairs
endothelial homeostasis, with the affected endothelium displaying a
hypercoagulant/prothrombotic/pro-oxidant state that hinders micro-
vascular reactivity [25]. The impaired microcirculatory blood flow,
together with the increased levels of inflammatory mediators, enhance
the mechanical stress of cardiomyocytes and metabolic demands of
conduction muscle cells, promoting metabolic instability and conduc-
tion disorders [26]. Moreover, SARS-CoV-2 genes may also encode K
channels and dysregulate the action potential and Ca2+ handin in
cardiomyocytes, while excessive inflammation can further modulate the
function of several ion channels, leading to QT prolongation and arr-
hythmias [1,15]. Further research is necessary for the elucidation of the
underlying mechanisms of bradycardia in patients with COVID-19.

Based on our experience, the use of drugs that increase pro-
inflammatory cytokine production or those affecting the conduction
system of the heart should be avoided in patients with the B.1.1.7
variant, especially in those with established sinus bradycardia or other
conduction disorders [27–31]. Moreover, the use of anticholinergics,
such as atropine, could inhibit the protective effects of the cholinergic
anti-inflammatory pathway. In these patients, transcutaneous or

Fig. 1. Clinical course of patients who developed bradycardia during hospi-
talization (first wave, n = 2; second wave, n = 62). All of them had bradycardia
by the time of intubation. ICU, intensive care unit.

Fig. 2. Average dose of isoprenaline and noradrenaline in our patients (n = 81). The dose of isoprenaline was significantly higher during the second wave
(p = 0.026) in contrast to this of norepinephrine (p = 0.051). ICU, Intensive Care Unit.

Average Dose

Drug
Isoprenaline
Noradrenaline

Timepoint
Pre
Intubation
Post
Intubation
ICU Admission
7 days
14 days
21 days
28 days
35 days
42 days
49 days
56 days
63 days
70 days
77 days
84 days
91 days
98 days
105 days
112 days
119 days
126 days
133 days
140 days
147 days
154 days
161 days
168 days
175 days
182 days
189 days
196 days
203 days
210 days
217 days
224 days
231 days
238 days
245 days
252 days
259 days
266 days
273 days
280 days
287 days
294 days
301 days
308 days
315 days
322 days
329 days
336 days
343 days
350 days
357 days
364 days
371 days
378 days
385 days
392 days
399 days
406 days
413 days
420 days
427 days
434 days
441 days
448 days
455 days
462 days
469 days
476 days
483 days
490 days
497 days
504 days
511 days
518 days
525 days
532 days
539 days
546 days
553 days
560 days
567 days
574 days
581 days
588 days
595 days

transvenous pacing may be ineffective or unavailable and isoprenaline should be the first line medication for the treatment of bradycardia, especially before endotracheal intubation [30]. Moreover, isoprenaline induces vasodilatation through β2 adrenoceptor stimulation in arteriolar smooth muscle and may improve microvascular blood flow and tissue oxygenation [32].

The study has several strengths. It is a multicenter study that relied on collection of clinical, laboratory, and outcome data throughout the COVID-19 hospitalization during two successive outbreak waves, capturing a diverse patient population. Data collection was systematic and all patients admitted/intubated during the period April 1st to December 31st 2020 were enrolled. Our sample was limited to patients consecutively hospitalized specifically for COVID-19 and without receiving any specific treatment besides dexamethasone, allowing for a better description of the effects of SARS-CoV-2 infection on different organs of the human body. The major limitations of the present study are the relatively small sample and its observational nature. Despite the careful analysis, it is not possible to fully account for all potential confounders and therefore, the study cannot be trusted per se as a basis of clinical decision. However, our findings have significant implications for a better understanding of the pathophysiology of COVID-19 and for better planning and organization in the future.

5. Conclusions

Development of bradycardia during hospitalization was associated with poor outcome. As B.1.1.7 variant strain is spreading more rapidly in many countries, our findings are important and can help in the classification of novel COVID-19 phenotypes for identifying populations that may benefit from early admission to ICU.

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