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Relative bradycardia in patients with moderate-to-severe COVID-19: a retrospective cohort study

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Abstract

Coronavirus-related disease (COVID-19) can result in relative bradycardia; however, there are no reports on relative bradycardia in patients with moderate-to-severe COVID-19 who require oxygen. We retrospectively investigated 45 patients with moderate-to-severe COVID-19 and examined the relationship between heart rate and body temperature at the time of initiating oxygen or mechanical ventilation. For three consecutive days after initiating oxygen therapy, body temperature (day's highest temperature), heart rate, and other vital signs were measured simultaneously. We checked for relative bradycardia and analyzed the differences between patients with moderate COVID-19 (oxygen requirement ≤ 5 L/min) and those with severe COVID-19 (oxygen requirement ≥ 5 L/min). Of the 45 patients, 28 and 17 had moderate and severe COVID-19, respectively. The heart rate increased with increasing body temperature, and almost all patients satisfied the criteria of relative bradycardia. In Spearman's rank correlation analysis, body temperature was significantly correlated with heart rate ($\rho = 0.483$, $p = 0.012$) in moderately ill patients but not in severely ill patients ($\rho = 0.261$, $p = 0.297$). Multiple regression analysis revealed that the severity of COVID-19 and body temperature were independent predictors of heart rate. The predicted change in heart rate was 6.0 beats/min for each 1 °C rise in body temperature. Relative bradycardia was suggested to be a characteristic finding in patients with moderate-to-severe COVID-19 who require oxygen. Additionally, severely ill patients were more likely to develop relative bradycardia than moderately ill patients. Focusing on the relationship between heart rate and body temperature might help clinicians diagnose this disease in patients with worsening respiratory failure.

Keywords COVID-19 · Relative bradycardia · Respiratory failure · Heart rate and body temperature relationship

Introduction

Heart rate (HR) usually increases by approximately 18 beats/min for each 1 °C rise in body temperature (BT) [1]. However, in certain infectious diseases, HR does not increase as expected; this phenomenon is known as relative bradycardia (RB). Previous reports have demonstrated that some patients with the coronavirus-related disease (COVID-19) have RB and that the condition of patients with COVID-19 may suddenly worsen and they may require oxygen approximately 7 days after onset of symptoms [2–6]. Nakamura et al. reported that two patients with severe COVID-19 had RB when they needed oxygen therapy [5]. However, except for those cases, there have been no reports investigating whether RB in patients with COVID-19 coincides with increased oxygen demand. Therefore, we examined the HR-BT relationship at the time of initiating oxygen therapy or mechanical ventilation in patients with moderate-to-severe COVID-19 who required oxygen therapy and investigated RB in these patients. We compared the data between patients with moderate and those with severe COVID-19.

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Materials and Methods

Study Design and Participants

We retrospectively reviewed the medical records of 89 patients who were admitted to our hospital between March 2020 and March 2021 with confirmed COVID-19 based on the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using polymerase chain reaction or loop-mediated isothermal amplification. Of the 89 patients, we investigated 45 patients with moderate and severe COVID-19 who required oxygen therapy. We excluded patients who did not require oxygen therapy, and those with arrhythmia and pacemaker rhythm as well as those in whom β-blockers and catecholamines were used during the survey period.

Oxygen therapy was initiated when oxygen saturation (SpO2) was ≤ 93% at rest. Intubation and mechanical ventilation were initiated when SpO2 was ≤ 90% with oxygen rate of 5 L/min. High-flow nasal oxygen therapy was done for the severely ill patients who did not intubate. According to Japanese guide for front-line healthcare workers [7], we defined the patients with oxygen requirement ≤ 5 L/min as moderate COVID-19 and the patients with oxygen requirement ≥ 5 L/min as severe COVID-19. Patients who were started on oxygen therapy were routinely administered dexamethasone (6 mg/day) and unfractionated heparin for 10 days. Almost all patients were administered antiviral drugs such as remdesivir unless they were contraindicated. For 3 consecutive days from the day of initiating oxygen therapy, BT (daily highest value) and other vital signs were measured simultaneously. RB was determined based on the definition of Cunha et al. [1].

This study was approved by the Gifu Prefectural General Medical Center Ethics Committee (approval no. 649). The requirement for informed consent was waived because of the retrospective nature of the study.

Statistical Analysis

The patients were divided according to the severity of COVID-19. Continuous data were expressed as median and interquartile range and categorical data, as frequencies and percentages. The baseline characteristics of each group were analyzed using the Mann–Whitney U test for continuous data and Fisher's exact test for categorical data. Statistical significance was set at $p < 0.05$.

The relationships between HR and other vital signs, such as BT, respiratory rate, and SpO2, were tested using Spearman's rank correlation as univariate analysis. Covariates with $p < 0.05$ on univariate analysis were analyzed using multivariate regression analysis along with age, sex, and severity to identify independent predictors of HR. The average value of each vital sign over 3 days was used for these analyses.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to include statistical functions used in biostatistics [8].

Results

Characteristics of Patients (Table 1)

Of the 45 patients analyzed, 28 patients had moderate illness and required oxygen at 5 L/min or less, and 17 patients had severe illness and required oxygen at 5 L/min or more (high-flow nasal oxygen therapy, $n = 3$; intubation and mechanical ventilation, $n = 12$; extracorporeal membrane oxygenation [ECMO], $n = 2$).

The overall median age was 71 years, and the proportion of men was 64%. There was no significant difference in the age or sex distribution between the moderate and severe groups. Body mass index, history of smoking, and the number of days between the onset of symptoms and hypoxia also demonstrated no significant differences between the groups. Vital signs were measured at the same time for 3 days since initiating oxygen therapy. Among the vital signs, only HR demonstrated a significant difference between the groups (overall median HR, 71 [68–85] bpm; moderate group, 77 [68–85] bpm; severe group, 67 [62–72] bpm; $p = 0.006$). There was no significant difference in the comorbidities except for the diabetes (moderate group, 14% vs severe group, 53%; $p = 0.008$). In laboratory and physiological parameters, the median C-reactive protein (CRP) level was 5.6 (1.7–8.3) mg/dL, lactate dehydrogenase (LDH) level was 318 (233–380) U/L, and D-dimer level was 1.1 (0.9–2.0) µg/dL. These values were significantly different between the two groups. In contrast, white blood cell count, hemoglobin, brain natriuretic peptide (BNP) level, troponin-I levels, and ejection fraction of echocardiography were not significantly different between the two groups. In medications, there was no significant difference in the content, and amount of steroids since dexamethasone 6 mg/day was administered uniformly. And unfractionated heparin was also used routinely, so no significant difference was observed as well. As for the antiviral drugs, remdesivir and favipiravir were used, but neither was significantly different between the two groups.

Table 1 Characteristics of patients

Characteristics	Total ($n=45$)	Moderate ($n=28$)	Severe ($n=17$)	p-value
Age, years old	71 [60–80]	69 [58–80]	72 [63–76]	0.656
Sex, men	29 (64)	16 (57)	13 (76)	0.219
Body mass index, kg/m^2	24.3 [21.7–26.6]	22.9 [20.8–25.6]	25.0 [24.1–27.1]	0.094
History of smoking	22 (49)	12 (43)	10 (59)	0.365
Days from symptom onset to hypoxia	7 [4−8]	6 [4−8]	8 [5−8]	0.193
Vital signs[#]				
Heart rate, bpm	71 [63–81]	77 [68–85]	67 [62–72]	0.006
Mean blood pressure, mmHg	86 [76–97]	86 [75–99]	88 [77–91]	0.752
Respiratory rate/min	20 [16−22]	20 [18−22]	20 [15−23]	0.288
Body temperature, °C	37.4 [37.1–37.9]	37.4 [37.0–37.8]	37.6 [37.1–37.9]	0.461
SpO2*, %	95 [94–96]	95 [95–96]	95 [92–96]	0.110
Comorbidities				
Hypertension	15 (33)	9 (32)	6 (35)	1.000
Hyperlipidemia	14 (31)	8 (29)	6 (35)	0.744
Diabetes	13 (29)	4 (14)	9 (53)	0.008
COPD**	6 (13)	5 (18)	1 (6)	0.385
Cardiovascular disease	4 (9)	4 (14)	0 (0)	0.281
Renal failure	4 (9)	3 (11)	1 (6)	1.000
Laboratory findings at admission				
White blood cell count, uL	5100 [3800–7000]	4650 [3575–5925]	5800 [5000–8200]	0.066
Hemoglobin, g/dL	13.3 [12.2–14.5]	13.2 [11.9–14.5]	13.6 [12.7–14.5]	0.343
Lactate dehydrogenase, U/L	318 [233–380]	283 [223–329]	381 [287–512]	0.006
C-reactive protein, mg/dL	5.6 [1.7–8.3]	3.5 [1.3–6.8]	8.3 [6.0–10.8]	0.002
D-dimer, ug/dL	1.2 [0.9–2.5]	1.1 [0.8–1.5]	1.8 [1.3–3.4]	0.002
BNP*[#], pg/mL	15.4 [7.2–40.3]	11.2 [5.8–46.3]	20.9 [10.6–31.9]	0.416
Troponin I, ng/mL	0.01 [0.01–0.02]	0.01 [0.01–0.02]	0.01 [0.01–0.02]	0.709
Physiological findings at admission				
Ejection fraction, %	62 [60–64]	63 [62–66]	61 [60–62]	0.386
Medications				
Dexamethasone	40 (89)	25 (89)	15 (88)	1.000
Unfractionated heparin	37 (82)	22 (79)	15 (88)	0.690
Remdesivir	30 (67)	18 (64)	12 (71)	0.752
Favipiravir	10 (22)	6 (21)	4 (24)	1.000
Sedation	10 (22)	0 (0)	10 (59)	< 0.001
Treatments				
High flow nasal oxygen therapy	3 (7)		3 (18)	
Intubation and MV[#]*	12 (27)		12 (71)	
ECMO[##]	2 (4)		2 (12)	

Values are median [range] or no. (%)

[#]Vital signs were measured at the same time (the highest point of the body temperature) for 3 consecutive days from the day when oxygen therapy was started

*SpO2 percutaneous oxygen saturation; **COPD chronic obstructive pulmonary disease; *[#]BNP brain natriuretic peptide; [#]*MV mechanical ventilation; [##]ECMO extracorporeal membrane oxygenation

Finally, sedatives were significantly different between the two groups ($p < 0.001$) because the use of sedatives was essential during ventilator management. The combination of midazolam and fentanyl was mainly used, but only one case used the combination of propofol and fentanyl.

Correlations Between HR and Vital Signs (Table 2) (Figs. 1,2)

In Table 2, we show the correlations between HR and other vital signs. As shown in Table 2, only BT correlates with

Table 2 Correlation between heart rate and other vital signs by Spearman's rank correlation analysis

Variable	Total		Moderate		Severe	
	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value
Body temperature, °C	0.296	0.050	0.483	0.012	0.261	0.297
Respiratory rate/min	0.271	0.075	−0.046	0.825	0.552	0.026
Mean blood pressure, mmHg	0.128	0.402	0.257	0.186	−0.049	0.851
SpO2*, %	−0.141	0.391	−0.050	0.809	−0.520	0.069

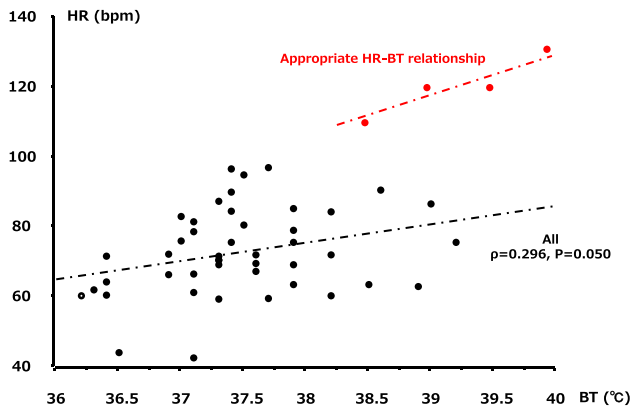*$SpO2$ percutaneous oxygen saturation

Fig. 1 The HR-BT relationship of all patients with COVID-19 (all: black dots and line); correlations were tested by spearman's rank correlation analysis ($\rho = 0.296$, $p = 0.050$)
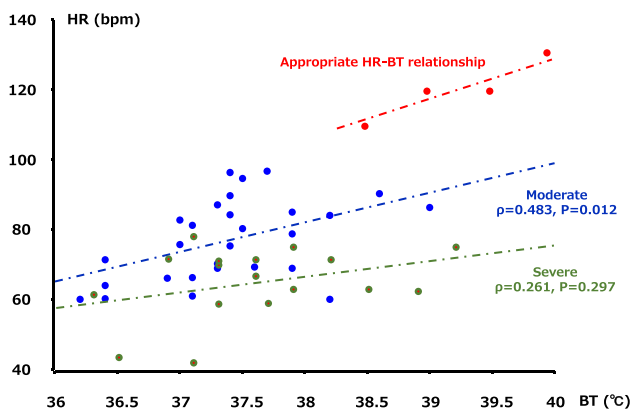

Fig. 2 The HR-BT relationship of the patients with moderate and severe COVID-19 (moderate: blue dots and line, severe: green dots and line); correlations were tested by Spearman's rank correlation analysis (moderate: $\rho = 0.483$, $p = 0.012$, severe: $\rho = 261$, $p = 0.297$). The red line depicts the predicted and appropriate HR-BT relationship based on Cunha's criteria (red dots: points of HR-BT relationship shown in Cunha's criteria). Abbreviations; HR: heart rate, BT: body temperature, COVID-19: coronavirus-related disease

HR ($\rho = 0.296$, $p = 0.050$) significantly among vital signs. Considering the severity of COVID-19, in the moderate group, BT was significantly correlated with HR ($\rho = 0.483$, $p = 0.012$), and in the severe group, only respiratory rate was significantly correlated with HR ($\rho = 0.552$, $p = 0.026$).

The HR-BT relationship observed in this study is presented in Fig. 1, which shows that HR tended to increase with increases in BT. Almost all plots were below the predicted HR-BT relationship based on the criteria of Cunha et al. [1]. In Fig. 2, in the moderate group, BT is significantly correlated with HR ($\rho = 0.483$, $p = 0.012$); however, in the severe group, BT is not significantly correlated with HR ($\rho = 0.261$, $p = 0.297$). This finding indicates that compared with the moderate group, the severe group was less likely to have increased HR and was more likely to develop RB.

Multivariate Analysis (Table 3)

Multiple regression analysis revealed that the severity of COVID-19 and BT were independent predictors of HR. On multivariate regression analysis, the predicted change in HR was 6.0 beats/min for every rise in BT of 1 °C.

Discussion

In the present study, we noted two clinically important observations. First, we demonstrated that almost all patients with moderate-to-severe COVID-19 had RB according to Cunha's criteria [1]. Second, the severely ill patients had lower HR than moderately ill patients with increases in BT, which indicates that severely ill patients are more likely to develop RB than moderately ill patients.

First, this study demonstrated that almost all patients with moderate-to-severe COVID-19 had RB according to Cunha's criteria [1]. Our data showed that a predicted change in HR was < 18 beats/min for each 1 °C increase in patients with COVID-19. Gioele et al. reported that 56% of patients with COVID-19 had RB [6]. They defined RB as an inappropriate response that was not commensurate with fever. However, they reported that almost all cases developed RB, which was defined by Cunha's criteria; therefore, their results are comparable to ours. Many infectious and non-infectious causes of RB in febrile patients have been described; however, the pathogenesis of this phenomenon remains unknown. Direct pathogenic effects on the heart, especially the sinoatrial

Table 3 Association between heart rate and other characteristics (significant vital signs, age, sex, and severity) for coronavirus related disease patients, by multiple regression analysis

Variable	Unstandardized coefficients			Standardized coefficients	T	p-value	95% Confidence interval for B		VIF*
	B	Std. error		Beta			Upper	Lower	
Constant	− 172.148	82.844		-	− 2.078	0.045	− 339.856	− 4.439	-
Age, year	0.033	0.106		0.039	0.313	0.756	− 0.181	0.248	1.033
Sex, men	1.162	3.266		0.046	0.356	0.724	− 5.450	7.774	1.059
Body temperature, °C	5.981	2.227		0.361	2.686	0.011	1.473	10.490	1.060
Respiratory rate/min	0.485	0.425		0.142	1.141	0.261	− 0.375	1.345	1.093
Severity, moderate	11.911	3.308		0.493	3.601	<0.001	5.215	18.608	1.113

*VIF variance inflation factor

node, and the effects of inflammatory cytokines, such as interleukin-6 (IL-6), are among the proposed mechanisms of RB [9]. SARS-CoV-2 can have toxic effects on the nervous system [10], which can disturb the autonomic control of HR. Angiotensin-converting enzyme 2, which is the receptor for SARS-CoV-2, is expressed in cardiac cells [11]. Peigh et al. reported two cases of new-onset and persistent sinus node dysfunction associated with COVID-19, and the potential underlying mechanisms include myocardial inflammation or direct viral infiltration [12]. Additionally, increased levels of inflammatory cytokines, such as IL-6, which have been reported in patients with COVID-19, can increase the vagal tone and decrease HR variability [9, 13, 14]. Puntmann et al. demonstrated that cardiovascular magnetic resonance revealed cardiac involvement in 78% of patients and ongoing myocardial inflammation in 60% of patients in a cohort of German patients who had recently recovered from COVID-19 infection [15]. Therefore, RB might be associated with not only sinoatrial node dysfunction due to direct viral effects but also myocardial injury due to inflammatory cytokines. RB might reflect a characteristic inflammatory response to COVID-19, which directly or indirectly affects the cardiovascular system.

Second, this study demonstrated that patients with severe COVID-19 had lower HR than those with moderate COVID-19 following increase in BT, which indicates that severely ill patients are more likely to develop RB than moderately ill patients. In this study, CRP, LDH, and D-dimer levels were significantly higher in patients with severe illness than those in moderately ill patients. This suggests that patients with severe COVID-19 had hyperinflammatory and hypercoagulable conditions, which were caused by a cytokine storm due to SARS-CoV-2. IL-6 also appears to play an important role in the cytokine storm from SARS- CoV-2 [16]. High concentrations of IL-6 form a complex with the IL-6 receptor in the serum and are trans-signaled with gp130, which serves as a signal transducer of IL-6. It activates and impairs vascular endothelial cells, suppresses the contractility of cardiomyocytes, promotes the coagulation cascade, and increases tissue hypoxia and vascular permeability [17]. Therefore, IL-6 is deeply involved in the development of acute respiratory distress syndrome, shock, multiple organ failure, and disseminated intravascular coagulation [18]. IL-6 has been reported to demonstrate the strongest correlation with depressed HR variability, which may predict RB [14]. Previous reports have demonstrated that IL-6 concentrations were 3.6 times higher in patients with severe or critical COVID-19 than those in patients with mild COVID-19 [18]. IL-6 was not measured in this study; however, severely ill patients are considered to have higher IL-6 levels than moderately ill patients. The differences in IL-6 levels between the groups might have resulted in the differences in their HR responses. Therefore, we speculate that RB in COVID-19 may be related to the severity of illness. Additionally, troponin-I and BNP values measured at admission were not significantly different between the moderate and severe groups in this study. As described above, it has been reported that COVID-19 potentially causes cardiac damage [15]; therefore, focal myocardial damage caused by COVID-19 might affect the function of the sinus node. However, it was difficult to predict HR variability using these general cardiac markers based on the results of this study.

Further research is needed to assess our findings in a larger population of patients with COVID-19 of different severities. This will allow for further assessments of RB as a potential clinical sign of COVID-19 and its treatment implications. In recent years, tocilizumab (an IL-6-selective inhibitor) has been used in the treatment of COVID-19 [19,

20]. When IL-6-selective inhibitors are used in the future, attention should be paid to the variability in HR because HR may be altered by the suppression of IL-6 expression.

A limitation of this study is that dexamethasone was started at the same time as oxygen therapy, which would have resulted in lowering of BT. Steroids are known to play a role in inducing bradycardia in a small proportion of patients [21]. This makes it difficult to investigate whether the HR response to fever was appropriate. Additionally, the effects of other medications, such as remdesivir [22], and medical treatments, such as mechanical ventilation or ECMO, have not been evaluated. Particularly, the use of sedatives associated with mechanical ventilation or ECMO can affect the HR as well. In patients without sedation, measurement of vital signs was performed in a calm and comfortable state to avoid an increase in heart rate due to arousal or excitement. However, the results of this study must be interpreted taking into account that sedation might affect heart rate. To rule out the effects of these factors, it is necessary to investigate the HR-BT relationship without any medications; however, this would be ethically difficult to perform in real patients.

Conclusion

RB was suggested to be a characteristic finding in patients with moderate-to-severe COVID-19 at the time of an increase in oxygen demand. Moreover, severely ill patients were more likely to develop RB than moderately ill patients. Focusing on the HR-BT relationship might help clinicians in diagnosing this disease when examining patients with worsening respiratory failure.

Data Availability The data that support the finding of this study are available from the corresponding author upon reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval The study was performed according to the regulations of the local ethics committee (Gifu Prefectural General Medical Center Ethics Committee: approval no. 649).

Consent to Participate Not applicable.

Written Consent for Publication Not applicable.

Informed Consent As this was a retrospective analysis, informed consent was not deemed necessary per the Gifu Prefectural General Medical Center Ethics Committee.

Conflict of Interest The authors declare no competing interests.

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