# Relative bradycardia in patients with COVID-19

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## Abstract

Introduction: Relative bradycardia(RB) is a relatively low heart rate response to rise in body temperature that occurs in several infectious diseases and can be an important clinical sign. In previous case reports, RB was presented in some patients with COVID-19. Objective and Methods: To investigate the correlation between temperature and heart rate, we retrospectively reviewed 249 febrile patients with documented COVID-19 patients. RB was defined as a rise in the heart rate (HR) from a basal HR of less than 10 beats/minute/°C rise in temperature. Results: In this study, the prevalence of RB in patients with COVID-19 was 60.6%. When the HR at peak temperatures for patients with COVID-19 were compared with reference valve (general temperature-heart rate response in infectious disease), our findings demonstrate a relatively lower heart rate at all peak temperatures recorded. Despite differences in HR response, there were not significant differences in clinical outcomes (pulmonary manifestation, ICU care, Death). Conclusion: Most patients with COVID-19 are associated with relative bradycardia, not related to clinical outcomes. RB in COVID-19 can be considered as the clinical features for differential diagnosis from other febrile conditions.

## Introduction

COVID-19 is known to cause variable extra-respiratory manifestations, including the cardiovascular system. Arrhythmia is one of the reported cardiac complications includes variable situations, from nonspecific electrocardiographic changes to serious arrhythmias in critically ill patients[1]. Early studies reported the incidence of arrhythmias in patients with COVID-19 to be as high as 16.7%[2].

Relative bradycardia (RB) is a relatively low heart rate response to every 1-degree rise in body temperature. RB is a clinical term that is often used in daily practice and the literature as a clinical sign for an individual patient and a characteristic of some infectious diseases. Recently, there has also been studies of bradycardia and relative bradycardia in patients with COVID-19 infection[3,4]. Interestingly, bradyarrhythmias, including RB were much more common in patients from Asian (up to 40%) compared with other races[5]. To investigate the correlation between heart rate and temperature, we retrospectively reviewed 249 febrile patients with documented COVID-19 patients.

## Method

We conducted a retrospective medical records' review of 249 patients (57.59±20.73, 49.8% male subjects) serologically diagnosed with COVID-19 by using reverse transcription PCR from February 2020 to June 2021 in a tertiary care referral hospital. Exclusion criteria were patients treated with heart rate lowering medications (e.g. non-dihydropyridine calcium channel blockers or beta blockers) or bradycardia associated with other specific medical conditions (e.g. electrolyte imbalance). The data were reviewed by trained physicians. The study protocol was reviewed and approved by the institutional review board (IRB) of Jeon-buk National University Hospital (IRB Number; CUH 2022-03-003).

Symptoms, vital signs, laboratory findings, chest images, and treatment during the hospital days were collected. Fever was defined as temperature greater than 37.8°C. Body temperature and febrile heart rate were reviewed on initial patient evaluation, before application of treatment. Basal body temperature and heart rate were assessed during afebrile phase after treatment. Although there is not uniform definition of RB, we defined it a priori as a rise in the heart rate from a basal heart rate of less than 10 beats/minute/°C rise in temperature. When a pulse increase greater than 10 beats/minute/°C were classified as general heart rate response (GHRR).

Categorical variables were described as frequency and percentages. Fischer's exact test was used to evaluate categorical variables. All continuous variables are described as means ± SD that were compared using Student's t test. All analyses were two tailed, with clinical significance defined as $P < 0.05$. All statistical processing was performed using SPSS-PC 25.0 (Statistical Package for the Social Sciences, SPSS-PC. Inc., Chicago, IL).

**Result**

This study showed the prevalence of RB in patients with COVID-19 was 60.6% (Figure 1A). When the heart rates at peak temperatures for patients with COVID-19 were compared with reference valve (general temperature-heart rate response in infectious disease), our findings demonstrate a relatively lower heart rate at all peak temperatures recorded (Figure 1B). Patients with RB group were significantly older (60.24 ± 18.41 years) and basal temperatures were not significantly different between the two groups. Although, the RB group had a significantly higher median resting heart rate and the RB group had a significantly lower heart rate than the GHRR group at maximal temperature (73.53 ± 13.73 Vs. 61.83 ± 11.06; $p < 0.001$), the opposite phenomenon was seen during maximal temperature, with relative bradycardia group achieving significantly lower heart rates than the GHRR group (78.91 ± 14.36 Vs. 93.63 ± 17.12; $p < 0.001$) (Table 1). Despite differences in heart rate response, no significant differences were seen in clinical outcomes (pulmonary manifestation, ICU care, Death) (Table 1).

**Discussion**

In this study, prevalence of RB in patients with COVID-19 was 60.6%. This rate was higher than previous reports. Capoferri et al reported 110 hospitalized COVID-19 patients in which 36% developed relative bradycardia and of the patients with a fever 56% developed relative bradycardia[6].

The impact of COVID-19 infection on the cardiovascular system and connection with bradycardia is likely multifactorial that varies with disease severity as well as clinical setting. One of the most popular theories stems to the association of coronavirus and the angiotensin-converting enzyme 2 (ACE2) receptors[7]. It is likely that coronavirus has an inherent ability to invade the myocardial tissue. Although the mechanism of relative bradycardia is unclear, a hypothesis is that direct pathogen effects on the sinoatrial node and increased levels of inflammatory cytokines, such as interleukin-6, which was reported for patients with COVID-19, can increase vagal tone and decrease heart rate variability[8].

RB is a clinical term that is often used in daily practice and the literature as a clinical sign for an individual patient and a characteristic of some infectious diseases. The term has been defined in several studies[9] and can be an important diagnostic finding for variety of infectious diseases including Legionnaires' disease, typhoid fever, psittacosis, typhus, leptospirosis, malaria, and babesiosis. RB may be used to differentiate among infectious diseases in specific clinical situations. Because the prevalence of RB in patients with COVID-19 was up to 60.6% in this study, it could also be used as a specific clinical feature to differentiate among similar infectious conditions.

In this study, basal heart rate was higher in the RB group than the GHRR group whereas the maximal heart rate was higher in the GHRR group. RB group were older than GHRR group. This findings were consistent with previous studies that presented most cases occurred in patients over the age of 65[10]. The RB did not seem to affect clinical outcomes in this study. This result may suggest that RB caused by COVID-19 does not mean critical cardiac manifestation.

In conclusion, most patients with COVID-19 are associated with RB, not related to clinical outcome. RB in COVID-19 can be considered as the clinical features for differential diagnosis from other febrile conditions.

**Figure legend**

Figure 1 A. Distribution of Δheart rate/Δtemperature by group. B. Temperature – Heart rate relationship in patients with COVID-19 at peak temperatures (red spot and line: reference value (General relationship in infectious disease) adopted from *Emerging infectious diseases 2007;13:650.* and *infect Dis practice 1997;21:38-40.*

Figure 2. Vital sign chart in patient with COVID-19 (#125, median value)

Table 1. Clinical data and outcomes

| | RB (n=151) | GHRR (n=98) | p-value |
|---|---|---|---|
| Gender (male) | 77 (51.0%) | 47 (48.0%) | 0.698 |
| Age | 60.24 ± 18.41 | 53.52 ± 23.47 | 0.018 |
| Basal temperature (°C) | 36.07 ± 0.22 | 36.10 ± 0.23 | 0.380 |
| Maximal temperature (°C) | 37.90 ± 0.59 | 37.85 ± 0.49 | 0.480 |
| Basal heart rate | 73.53 ± 13.73 | 61.83 ± 11.06 | <0.001 |
| Heart rate at maximal temperature | 78.91 ± 14.36 | 93.63 ± 17.12 | <0.001 |

| | RB (n=151) | GHRR (n=98) | p-value |
|---|---|---|---|
| Pulmonary involvement on radiologic test | 103 (68.2%) | 68 (69.4%) | 0.889 |
| ICU care | 35 (23.3%) | 29 (29.6%) | 0.300 |
| Death | 8 (5.3%) | 3 (3.1%) | 0.534 |

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**Competing interest**

There are no conflicts of interest.

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