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# Beyond slow pulse: Systematic review of relative bradycardia in clinical practice

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## Abstract

**Introduction:** Relative bradycardia, also known as Faget's sign, occurs when the heart rate does not increase in proportion to fever. Although it has been described for years in different infections, in daily practice it is rarely sought systematically and its clinical usefulness is not always taken into account.

**Objective:** To determine whether relative bradycardia is useful in guiding diagnosis and prognosis in patients with febrile syndrome.

**Methods:** A systematic review of the literature was conducted in PubMed, Scopus, Web of Science, and SciELO. Articles published between 1992 and 2024 that evaluated the relationship between body temperature and heart rate were included.

**Results:** Twenty-four studies were included. Relative bradycardia was most frequently described in typhoid fever, dengue, legionellosis, and leptospirosis. Most studies showed high specificity, although sensitivity was variable. Its identification helped to better guide diagnosis, especially in resource-limited settings. Variability was also found between studies.

**Conclusions:** Relative bradycardia is a clinical sign that can be useful in daily practice but is underutilized. Its value could be improved by standardizing diagnostic criteria and conducting more prospective studies.

**Keywords:** Relative bradycardia; Faget's sign; Fever; Infectious diseases; Systematic review

## 1. Introduction

In a very rare event called relative bradycardia or Faget's sign, fever is accompanied by a reduction in heart rate, rather than the expected increase (all febrile patients show an increase in heart rate of 8- 10 beats/min for every degree Celsius above 38.3 °C); therefore, there is a gap between body temperature and the expected chronotropic response (1). This sign was first reported in the late 19th century in patients with typhoid fever, and subsequently reevaluated in clinical series associating this symptom with specific infections (3). Subsequently, there has been a growing correlation with

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several other pathologies and infections such as CNS tumors, drug treatment (beta-blockers), legionellosis, brucellosis, leptospirosis, dengue, psittacosis, and yellow fever (10,14). However, today it is not highly valued in clinical practice. This is undoubtedly due to the rapid and highly sensitive nature of the diagnostic tests (whether PCR or specific serologies) that we now have and that have replaced the importance of a thorough clinical examination. When resources are limited, clinical evaluation remains the cornerstone. In such cases, the recognition of relative bradycardia can be very useful, because it is an easily obtained non-invasive finding at no additional cost. The problem, however, is that no one knows how to define it (studies differ in their cut-off points), and the confusion complicates its use in clinical practice. Other definitions are in the range of 8-10 beats (increase in

bpm, per degree > 38°C), which supports the variation identified in the literature. In addition, many conditions other than fever can affect heart rate, such as beta-blocker use, metabolic changes, autonomic nervous system dysfunction, hypoxia, pain, dehydration, endocrine diseases, etc. All of this makes the meaning of the sign difficult to interpret reliably and explains the variability in sensitivity and specificity reported in studies. However, some studies found that relative bradycardia could inform the differential diagnosis of fevers, particularly in intracellular pathogens, including *Legionella pneumophila, Coxiella burnetii, Salmonella typhi, Brucella spp. or Leptospira interrogans* (3,10,14). But the data are mixed, across studies of varying study designs, methodological quality, and sample sizes, resulting in ongoing debate about its true clinical utility. These factors make systematic review the best attempt to summarize the available evidence on relative bradycardia in clinical practice and its prognostic value. It also aims to identify what remains to be defined and what still needs to be studied to better elucidate the functional role of this sign in febrile patients (22).

## 2. Methodology

A systematic review of the literature was conducted, following the PRISMA 2020 guideline. An exhaustive search was performed in the PubMed/MEDLINE, Scopus, Web of Science, and SciELO databases for articles published between January 2000 and December 2024. Observational cohort, case-control, cross-sectional, and case series studies evaluating the presence of relative bradycardia in the context of infectious diseases were included. One hundred records were identified, and after removing duplicates, 82 remained. Titles and abstracts were scanned, and 40 studies were excluded based on the following exclusion criteria:

- Studies that did not analyze relative bradycardia or did not clearly define the phenomenon.
- Single case reports, letters to the editor, comments, narrative reviews without primary data.
- Studies that included only pediatric populations, with the exception of comparative studies with adults
- Articles with insufficient data to be extracted or without access to full text or insufficient methodology.
- Studies that analyzed heart rate as a sign of fever but did not associate it with an infectious cause.

Forty-two full-text articles were reviewed, of which 18 were subsequently excluded for failing to meet methodological quality criteria, lack of operational definition of relative bradycardia, or lack of comparable data. Finally, 24 studies were included in the review. The selection was made independently by two reviewers. Methodological quality was assessed using the Newcastle-Ottawa scale. No meta-analysis was performed due to the clinical and methodological heterogeneity of the studies.

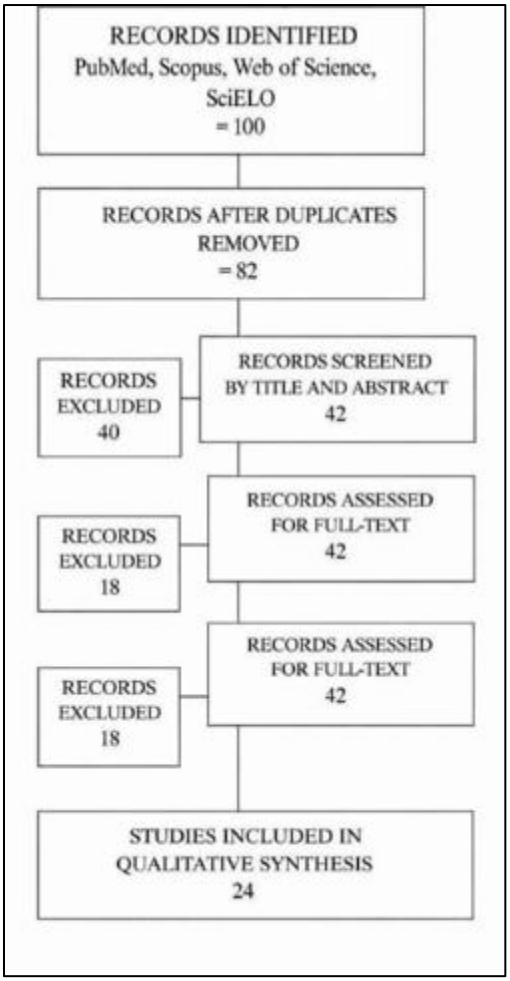


**Figure 1** PRISMA flow diagram showing the process of identification, selection, eligibility, and inclusion of studies in the systematic review on relative bradycardia

## 3. Development

The review included articles from Asia, Europe, and America; all reported that relative bradycardia is a clinical sign found in various epidemiological situations (1,4,3). Classic studies by Cunha, Fan Ye, and more recent series such as those by J. Bolaños Guedes et al. show that it is not a rare event (1,4,16) and that contextual factors such as the type of predominant infection or the characteristics of the population probably influence it. In terms of methodological designs, most were observational studies, retrospective cohorts, cross-sectional studies, and some case series (such as those by Wittesjo, Cunha, and Ostergaard) were the most common designs (5,1,3). Sample sizes varied greatly between studies, ranging from a few cases to large cohorts, which may explain why the results were not always comparable or equally accurate (7,14).

The association between relative bradycardia and infections was evident in most articles. In typhoid fever, it is uniformly reported by Cunha, Wittesjo, and Fan Ye (1,5,4). It was also reported in dengue, legionellosis, leptospirosis, and brucellosis, with evidence from these same authors supporting its association with highly inflammatory febrile illnesses (10,11,14,16). One aspect on which almost all studies agreed was the lack of a common definition. Some used traditional criteria for the expected response of heart rate to fever, as proposed by Cunha (1,12,13), while others used fixed cut-off points or age-adjusted equations, creating great heterogeneity (4,5).

There are multiple pathophysiological hypotheses, involving autonomic mechanisms, mediated by proinflammatory cytokines, and even by the direct action of certain pathogens on the conduction system. These ideas are found in Cunha's writings, but the evidence is more theoretical than definitive (1,4,23). In terms of diagnostic accuracy, most studies found low sensitivity but acceptable specificity in situations with a high prevalence of related infections (21,15).

Certainly, autonomic dysfunction was also investigated as one of the main pathophysiological mechanisms, with changes in variability associated with febrile infections such as dengue, showing information on transient suppression of sympathetic tone or excessive vagal activation (23). The

modification of the autonomic response could explain the lack of compensatory tachycardia in cases of high body temperature. It is important to note that other recent studies have shown evidence of subclinical myocardial abnormalities and conduction disorders due to viral and bacterial infections, indicating a direct impact of microorganisms or their toxins on the sinus node or the cardiac electrical system (18,19). Added to this process is the role of inflammatory mediators such as interleukins, especially IL-1β, IL-6, and TNF-α, which can modify autonomic activity and decrease (or even block) the chronotropic response and cardiac ion conductance, thus reinforcing that relative bradycardia is inflammatory and neurocardiogenic. Taken together, these findings provide evidence that relative bradycardia is a complex, multifactorial pathophysiological phenomenon involving autonomic, inflammatory, and cardiotropic pathways.

Differences between adults and the pediatric population were also evident. In children, studies such as that by Ostergaard et al. found greater variability, which could be explained by the wider physiological ranges of heart rate and common comorbidities in febrile conditions (3,6). Some authors analyzed clinical outcomes, such as duration of fever or need for hospitalization, but the findings were not consistent across studies (7,20).

In addition, the usefulness of relative bradycardia in different infectious scenarios has been investigated by some recent studies. In infections such as dengue, bradycardia, conduction disorders, and electrocardiographic changes have produced a variable spectrum of cardiovascular manifestations of infection, although their effect on overall prognosis remains undetermined (18, 20). A similar pattern of relatively high rates of bradycardia has been observed in SARS-CoV-2 infections, largely conceptualized as a phenomenon secondary to inflammatory and autonomic pathophysiological characteristics, but it cannot be considered an independent prognostic indicator (14, 15). Conversely, the literature describes that relative bradycardia can also be found in non- infectious conditions, and thus, the finding should be interpreted with caution. Pharmacological mechanisms are covered, particularly through beta-blockers, calcium antagonists, or digoxin, as well as autonomic dysfunctions observed in children with dengue and metabolic disorders that modulate the chronotropic response (22, 24). Based on these observations, the notion that relative bradycardia should probably be viewed from a multidimensional clinical perspective, not merely as an all-or-nothing statistic for infectious etiology, is reinforced (Table 1).

**Table 1** Infectious and non-infectious causes of relative bradycardia

| Category | Subtype | Examples | References |
|---|---|---|---|
| Infectious | Bacterial | *Salmonella typhi, E. coli bacteremia, babesiosis, Mycoplasma pneumoniae* | (1,7,9,16,24) |
| Infectious | Viral | Dengue, COVID-19, viral cardiac disorders | (10,11,14,15,18,20) |

Finally, a curious historical trend: while older studies gave it diagnostic value, more recent ones consider it a complementary sign (13,19). The availability of more sensitive tests has probably displaced its use in clinical practice. There are still significant gaps, such as the absence of prospective studies and established criteria, which prevent its inclusion in clinical practice guidelines (1,3,4).

## 4. Discussion

These findings corroborate that relative bradycardia occurs consistently across multiple infections, a fact that Cunha, Ostergaard, and recent studies such as that by Ye et al. have observed (1,3,4). Although its clinical utility has declined, having been somewhat overshadowed by current diagnostic methods, it remains an accessible and potentially useful indicator in the appropriate context (19). The major problem with standardization is that there is no clear definition. The proposed criteria for normality (particularly by Cunha, Ostergaard, and Ye's review) differ in equations, cut-off points, and age correction, making comparison between studies difficult and preventing it in clinical practice (1,3,4,5).

It is this methodological variability that makes it plausible: although it has been known as a diagnosable finding for decades, it has not yet emerged as a clear diagnostic criterion (20). Despite these limitations, however, most studies agree that its specificity can help facilitate the differential diagnosis of febrile conditions. For infections such as typhoid

fever, legionellosis, or dengue, the results of Davis et al. in children, Matono et al. in travelers, and Lateef et al. in dengue also point to its usefulness for some etiologies (6,7,11).

The main hypotheses for pathophysiology have focused on temporary vagal modulation, inflammatory cytokines, and even a direct impact of specific pathogens or toxins on the sinus node. Although their arguments have been debated in reviews such as those by Cunha and Ye, more

research is needed to confirm this mechanistic structure with greater confidence (1,4,23). This sign remains valuable, however, in regions lacking diagnostic tools (19).

Evidence from Davis' pediatric series and clinical reports by Matono and Lateef show that relative bradycardia, in the absence of available complementary tests, can facilitate diagnostic choice and early action during early detection of the disease (6,7,11). Recovering its teaching may be particularly valuable for primary care workers or those in rural areas with technological limitations (19).

It is also worth mentioning the factors that can distort its reading. Beta-blockers, electrolyte imbalance, dehydration, shock, or myocardial damage can modify the anticipated heart rate response, as demonstrated by clinical studies on cardiac involvement in dengue by Mansanguan et al. and Parchani et al. (22,24). This review demonstrates the common limitations of the literature: it is dominated by observational studies, has high methodological heterogeneity, and there are still no prospective studies designed to evaluate this phenomenon. These gaps have hindered its incorporation into current clinical guidelines (Cunha and Ostergaard) (1,3). Standardized definitions and more rigorous designs will be necessary to determine its diagnostic significance (1,4).

## 5. Conclusion

Overall, the review shows that relative bradycardia does exist; it is not a myth from old books, but its value depends greatly on the context. It does not appear in all febrile patients, nor does it behave uniformly, which explains why it does not currently occupy a central place in diagnosis. Even so, when identified at the right time and in the right patient, it can provide guidance, especially in infections that classically present it.

The biggest problem remains that no one speaks the same language to define it: each study uses its own criteria, its own ranges, and its own formulas. This makes it difficult to compare them and weakens the sign's value as a diagnostic tool. Added to this are common factors such as medications, comorbidities, and hydration status, which can alter the cardiac response and confuse interpretation.

Despite everything, relative bradycardia remains a clinical finding worth looking at. It cannot be used to rule out infections such as typhoid fever, Legionnaires' disease, or dengue, but it can add to the suspicion when the clinical picture points to them. In settings where access to diagnostic tests is limited, this simple detail can help refine the initial impression.

Ultimately, relative bradycardia should not be seen as an absolute criterion, but rather as an additional element of the physical examination. For it to play a more solid role, clear definitions and well- conducted prospective studies are needed. In the meantime, it remains a useful, simple clinical finding that can add value if interpreted judiciously.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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