The Clinical Significance of Relative Bradycardia

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ABSTRACT

Introduction: Relative bradycardia is a poorly understood paradoxical phenomenon that refers to a clinical sign whereby the pulse rate is lower than expected for a given body temperature.

Objective: To provide an overview and describe infectious and noninfectious causes of relative bradycardia.

Methods: PubMed and Medline databases were searched using individual and Medical Subject Headings terms including relative bradycardia, fever, pulse-temperature dissociation and pulse-temperature deficit in human studies published from inception to October 2, 2016. The causes and incidence of relative bradycardia were reviewed.

Results: Relative bradycardia is found in a wide variety of infectious and noninfectious diseases. The pathogenesis remains poorly understood with proposed mechanisms including release of inflammatory cytokines, increased vagal tone, direct pathogenic effect on the myocardium, and electrolyte abnormalities. The incidence of this sign varies widely, which may be attributable to multiple factors, including population size, time course for measuring pulse and temperature, and lack of a consistent definition used. The fact that this sign is not consistently identified in case series suggests that relative bradycardia is caused by mechanisms presumably involving or influenced by pathogen and host factors.

Conclusions: Relative bradycardia is a sensitive but nonspecific clinical sign that may be an important bedside tool for narrowing the differential diagnosis of potential infectious and noninfectious etiologies. Recognizing this relationship may assist the clinician by providing bedside clinical clues into potential etiologies of disease, particularly in the setting of infectious diseases and in circumstances when other stigma of disease is absent.

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INTRODUCTION

Under feverish conditions, for each Celsius degree increase in body temperature above 38.3° C (101° F) a corresponding rise in heart rate by 8 to 10 beats/minute is anticipated (Table 1). This finding was first described in the late 1800s by Carl von Liebermeister and is commonly referred to as Liebermeister's rule.[1] The inverse or paradoxical relationship between body temperatures above 38.3° C (101° F) with a pulse lower than expected for the degree of temperature elevation is referred to by the terms relative bradycardia, pulse-temperature dissociation (deficit) or Faget's sign. It has been suggested that relative bradycardia be only applied to cases where body temperature is >38.9° C (102° F), as it is difficult to detect meaningful differences between pulse and temperature at temperatures ≤38.9° C (102° F)[2] as the sign is most sensitive for temperatures > 38.9° C (102° F).[2] This clinical sign may be diagnostically important, particularly when used concomitantly with a detailed patient history, physical examination, and laboratory findings.

The pulse-temperature deficits that occur with relative bradycardia are observed in a limited number of both noninfectious and infectious (Table 2) diseases and conditions. In this review, we provide a comprehensive overview of this underrecognized clinical finding, including relevance to different disease states, diagnostic challenges, and exploration of the pathogenesis of relative bradycardia.

METHODS

PubMed and Medline databases were searched using individual and the following Medical Subject Headings terms: relative bradycardia, fever, pulse-temperature dissociation, and pulse-

Table 1. Expected Relationship Between Pulse and Temperature [1,23]

Temperature	Heart Rate With an Increase of 8 Beats/Minute	Heart Rate With an Increase of 10 Beats/Minute
38.3° C (101° F)	108	110
38.9° C (102° F)	116	120
39.4° C (103° F)	124	130
40.0° C (104° F)	132	140
40.6° C (105° F)	138	150
41.4° C (106° F)	146	160

Table 2. Infectious Causes of Relative Bradycardia (References available upon request)

Type of Infection	Microorganism Family	Infectious Agent	Disease
Bacterial	Chlamydiaceae	*Chlamydia pneumonia*	Chlamydial pneumonia
	Chlamydiaceae	*Chlamydia psittaci*	Psittacosis
	Coxiellaceae	*Coxiella burnetti*	Q fever
	Ehrlichiaceae	*Anaplasma phagocytophilum*	Human granulocytic anaplasmosis
	Ehrlichiaceae	*Ehrlichia chaffeensis*	Human monocytic ehrlichiosis
	Enterobacteriaceae	*Salmonella typhi, Salmonella paratyphi*	Typhoid fever
	Francisellaceae	*Francisella tularensis*	Tularemia
	Legionellaceae	*Legionella pneumophilia*	Legionnaire's disease
	Leptospiraceae	*Leptospira interrogans*	Leptospirosis
	Listeriaceae	*Listeria monocytogenes*	Listeriosis
	Mycobacteriaceae	*Mycobacterium tuberculosis*	Tuberculosis
	Rickettsiaceae	*Orientia tsutsugamushi*	Scrub typhus
	Rickettsiaceae	*Rickettsia rickettsia*	Rocky Mountain spotted fever
	Rickettsiaceae	*Rickettsia typhi*	Murine typhus
	Spirochaetaceae	*Borrelia burgdorferi*	Lyme disease
Parasitic	Babesiidae	*Babesia microti*	Babesiosis
	Plasmodiidae	*Plasmodium vivax, Plasmodium falciparum, Plasmodium*	Malaria
	Trypanosomatidae	*Trypanosoma cruzi*	Chagas disease
Viral	Arenaviridae	*Arenavirus*	Lassa fever
	Bunyaviridae	*Hantavirus*	Hemorrhagic fever with nephropathy
	Bunyaviridae	*Nairovirus*	Crimean-Congo hemorrhagic fever
	Bunyaviridae	*Phlebovirus*	Rift Valley fever
	Bunyaviridae	*Phlebovirus*	Sand fly fever
	Filoviridae	*Filovirus*	Marburg virus, Ebola hemorrhagic fever
	Flaviridae	*Flavivirus*	Yellow fever
	Flaviridae	*Flavivirus*	Dengue fever
	Flaviridae	*Flavivirus*	West Nile virus
	Picornaviridae	*Echovirus*	Acute meningitis
	Pneumoviridae	*Adult human metapneumonovirus*	Pneumonia

temperature deficit. The search was limited to human clinical studies in the English literature published prior to October 2, 2016. We also reviewed bibliographies of retrieved studies as well as reviews for additional relevant studies. Three reviewers independently screened titles, abstracts, and full text of potentially eligible articles to identify studies meeting inclusion criteria. Differences in inclusion were resolved through consensus adjudication. Information was obtained primarily from cohort studies, case series, or case reports. We identified 174 articles that met these criteria. Articles in this review were restricted to those that used the term relative bradycardia in the context of a temperature and pulse relationship, regardless of whether a case definition was applied or how the findings were diagnosed. An additional 21 studies were excluded that used the term relative bradycardia to describe the relationship between pulse and systolic blood pressure.

DISCUSSION

Terminology

Of all the articles identified in this review, the term relative bradycardia was confined to describe the inverse relationship between temperature and pulse rate. Thus, manuscripts that used the term relative bradycardia to describe the inverse relationship between systolic blood pressure and pulse rate in conditions such as trauma,[3-7] acute bleeding,[8-10] anaphylaxis,[11-13] autonomic response,[14-20] and hypovolemic shock [21] were excluded. We believe that the use of the term relative bradycardia in the context of systolic blood pressure-pulse dissociation is a misnomer and, therefore, should be limited strictly to those conditions that describe the inverse relationship between pulse and temperature[2,4,22,23] as originally described. Additionally, relative bradycardia should be applied only to patients in sinus rhythm. Hence, other conditions that slow atrial automaticity and atrioventricular conduction (eg, heart block medications such as antiarrhythmics [eg, amiodarone, digoxin], beta blockers and nondihydropyridine calcium channel blockers [eg, verapamil, diltiazem]), or that have a pacemaker-induced rhythm,[22,24-27] should be excluded from the case definition.

Table 3. Case Series of Relative Bradycardia

Condition	Definition	Total Cases	Cases Evaluated for Sign	% Cases Evaluated	Relative Bradycardia Frequency	% Relative Bradycardia Prevalence	Reference
Babesiosis	Heart rate less than corresponding degree of temperature elevation	17	9	53%	8	89%	47
Dengue	Not defined	50	50	100%	38	76%	56
Dengue	Not defined	24	13	54%	3	23%	57
Hantavirus-induced nephropathy	Heart rate of <90 bpm and fever	471	186	39%	149	80%	58
Legionnaire's disease	Heart rate ≤100 bpm with temperature ≥39.4° C	65	48	73%	28	60%	59
Legionnaire's disease	An increase in heart rate of less than 10 bpm/1° C increase in temperature, with the pulse rate ranging from 38.9° C to 41.1° C	13	13	100%	0	0	60
Legionnaire's disease	Not defined	17	17	100%	9	52.9%	61
Leptospirosis	Heart rate less than 10.2 times the temperature (°C) minus 333.	5	5	100%	5	100%	36
Malaria	Not defined	111	111	100%	15	13.6%	62
Murine typhus	Increase in heart rate <10 bpm for every 1° C increase in temperature	193	193	100%	94	49%	37
Q fever	Heart rate <110 bpm with temperature ≥38.9° C	109	60	55%	44	73%	40,41
Sandfly fever	Not defined	48	22	46%	5	23%	42
Scrub typhus	Increase in heart rate <10 bpm for every 1° C increase in temperature	100	100	100%	53	53%	46
Scrub typhus	Increase in heart rate <10 bpm for every 1° C increase in temperature	237	237	100%	92	38%	37,38
Tularemia	Heart rate <90 bpm over a base rate of 72 bpm for each 1° F temperature elevation	88	62	70%	26	42%	63
Typhoid	Not defined	30	30	100%	8	27%	64
Typhoid	Not defined	7	7	100%	1	14%	39
Typhoid	Not defined	130	101	78%	64	63%	65
Typhoid	A pulse rate less than 100 bpm even during a high fever	130	130	100%	62	48%	66

Abbreviation: bpm, beats per minute.

Conditions that cause degenerative, inflammatory, or infiltrative disease of the myocardium, slowing the ventricular rate, also may mimic relative bradycardia and should be excluded. Therefore, these conditions must be accounted for prior to diagnosis of relative bradycardia.

Causes of Relative Bradycardia

Noninfectious causes — Noninfectious causes of relative bradycardia include lymphoma,[2,22,28] drug-induced fever,[29-32] factitious fever, adrenal insufficiency, and cyclic neutropenia.[28] Drug fever is an obscure cause of fever and often is not considered in the initial differential diagnosis. It coincides temporarily with administration of a drug and disappears after discontinuation of the involved agent.[29-31] It is estimated that drug fever occurs in approximately 10% of hospitalized patients, particularly in the context of antimicrobial medications.[30] In one study, relative bradycardia was identified in 11 of 148 episodes in patients with drug-induced fever.[30]

In addition to relative bradycardia, other clinical clues that may suggest drug fever include lack of fever awareness and the absence of constitutional symptoms.[29-31] Similarly, factitious fever should be considered when patients present with fever and multiple hospitalizations in the absence of other constitutional symptoms. Finally, a case of cyclic neutropenia with periodic fever and relative bradycardia has been reported.[28] It has been proposed that granulocyte colony-stimulating factor (GCSF), IL 6 and tumor necrosis factor (TNF-α) may be involved in not only regulating hematopoiesis but also account for the finding of relative bradycardia in cyclic neutropenia.[28]

Infectious causes — Small sample size, lack of the use of a standard case definition, and reporting of signs limits the ability to draw conclusions regarding the incidence of relative bradycardia in certain infectious diseases. Relative bradycardia has been found to be a nonspecific yet sensitive sign of infection, particularly those caused by intracellular, nonenteric gram-negative organisms[33,34] and may be found early or late in the course of infection, or during the early convalescent period as described with leptospirosis[35,36] and typhoid fever.[37-39] It also may be a marker for delayed fever defervescence, despite appropriate treatment in patients with acute Q fever, scrub typhus, and murine typhus.[37,40,41]

In cases of typhoid fever caused by a gram-negative bacterium, relative bradycardia is identified infrequently in adults (15%-20%) and is absent in children.[34] In addition to infections caused by intracellular gram-negative pathogens, relative bradycardia also is seen in certain viral infections (eg, dengue and sandfly fever),[37,38,41,42] rickettsia bacterial (eg, anaplasmosis and ehrlichia),[43-45] parasitic protozoan (eg, malaria, babesiosis, and Chagas disease),[41,46-50] and leptospirosis (eg, spirochete bacteria) but not brucellosis infections.[2,35,36] It is hypothesized that Lyme disease may also present with relative bradycardia.[51-53]

In addition to dengue and sandfly fever, other viral hemorrhagic fevers (eg, Lassa fever, Rift Valley fever, Crimean-Congo hemorrhagic fever, Ebola hemorrhagic fever, Marburg virus disease, and yellow fever) also are associated with relative bradycardia.[27] Interestingly, dengue, yellow fever, and West Nile virus are all caused by the same RNA virus genus; of note, both Zika virus and tick-borne encephalitis virus are also members of this genus, however relative bradycardia has not been documented—to our knowledge—in these illnesses.[42,43]

Distinguishing Diagnostic Features of Relative Bradycardia Due to Infectious Disease

Differentiating the infectious cause of relative bradycardia can be, in some cases, a diagnostic challenge. These diseases share common presentations of nonspecific fever prodrome, along with constitutional symptoms such as malaise, fatigue, anorexia, chills, myalgia, and headaches. In some cases such as Legionnaire's disease and human granulocytic anaplasmosis, gastrointestinal symptoms including nausea, vomiting, and diarrhea may be present. In contrast, adults with typhoid fever commonly present with constipation.

Evaluation should begin with a thorough history including recent travel history to locations where pathogens are present, exposures to animals, consumption of contaminated water or food, and flea or tick bites. The presence of a rash and its location may provide additional information as to the disease etiology (eg, rose spots are found in 20% to 30% of adults with typhoid fever[28,54] and are confined to the chest, abdomen, and back, whereas the rash of Rocky Mountain spotted fever typically begins on the extremities and spreads to the trunk). The presence of pneumonia with relative bradycardia further narrows the differential diagnosis to Q fever, Legionnaire's disease, psittacosis, scrub typhus, or tularemia.[55] The absence of relative bradycardia in mycoplasma pneumonia and presence in Legionnaire's disease may be an important clinical clue for differentiating these two causes of community-acquired pneumonias. The presence of hepatitis, gastrointestinal symptoms, and pneumonia with relative bradycardia suggests Legionnaire's disease. Exposure to birds (psittacosis), ticks (Rocky mountain spotted fever, tularemia), placental products, or dried dust (Q fever) provide additional information to narrow the differential diagnosis. Thus, the use of this clinical sign if present, along with an accurate occupational, environmental, and avocational exposure history, provides additional clues for obtaining appropriate diagnostic confirmatory tests.

In the majority of case series shown in Table 3, relative bradycardia was typically observed in less than half of patients. However, it is important to note that for several infectious causes of relative bradycardia, not all cases were consistently evaluated for the presence of this sign. In studies where 100% of patients were evaluated, there was a broad range (0%-100%) reported for the incidence of relative bradycardia (Table 3). An important consideration with regard to these findings is that comorbidities, medications (eg, beta blockers, clonidine, and nondihyropyridine calcium channel blockers), and electrolyte abnormalities that may affect heart rate often were not reported. Indeed, hyponatremia, hyperkalemia, and hypokalemia are known to cause bradycardia, and hyponatremia is commonly identified in patients with relative bradycardia and Legionnaire's disease, scrub typhus, or Rocky Mountain spotted fever. Thus, relative bradycardia as a clinical sign may not have predictive value for obtaining a definite diagnosis, but may serve as a feature of specific diseases after other factors that cause bradycardia are accounted.

Pathogenesis of Relative Bradycardia

The incidence of this sign varies widely, which may be attributable to multiple factors including population size, the time course for measuring pulse and temperature, and lack of a consistent definition used. The fact that this sign is not consistently identified in case series suggests that relative bradycardia is caused by mechanisms presumably involving the pathogen and host factors, includ-

ing genetic determinants in response to infection.

The pathogenesis of relative bradycardia remains poorly understood and a variety of mechanisms have been proposed to explain this finding including release of inflammatory cytokines, increased vagal tone, direct pathogen effect on the myocardium, and electrolyte abnormalities. The systemic inflammatory response to infections is complex and involves the interaction of exotoxins and endotoxins from the pathogen and release of pro-inflammatory cytokines (IL 10, IL 6, IL 5, IL 2, IL1α, IL 17, IL 4), tumor necrosis factor alpha (TNFα), and granulocyte macrophage colony-stimulating factors from the host.[32] Some of these pro-inflammatory cytokines such as TNFα, IL 1 and IL 6 increase vagal tone decreasing heart rate. Conversely, vagal stimulation has been shown to decrease the levels of pro-inflammatory cytokines, thus modulating host response to infection.[33] Accentuated vagal response has been a proposed mechanism seen in some patients. Thus, inflammation, with its many mediators (eg, cytokines), can elicit in some patients a cascade of clinical signs and symptoms, including bradycardia, to eliminate potential threats to the host. These factors also are associated with activation of major systems (eg, cardiac, immunological, hematological, and neurological) responsible for systemic responses including bradycardia.

Our review had several limitations, including possibility of reporting biases. We may have missed published studies that were not in the English literature. Studies that we found may have selectively reported outcomes. Most of the studies had risks of bias due to unclear definitions and methods. The lack of a consistent standard for case definition also limited our ability to identify the actual incidence of this sign in various diseases.

CONCLUSION

Relative bradycardia is an underrecognized and underappreciated physical finding. Its recognition can be an important bedside tool for diagnosing infectious and noninfectious etiologies. Relative bradycardia may be a useful marker for diagnosis when other signs and symptoms are confusing or less clear to reveal disease etiology. More research is needed to determine the frequency of this finding in various infections and noninfectious diseases as well as its clinical significance in diagnosis and outcomes. Future reporting also should provide details about methods, apply consistent case definition of relative bradycardia, and specify a priori how outcomes will be measured.

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