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# Proposed mechanisms of relative bradycardia

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A B S T R A C T

Relative bradycardia is the term used to describe the mechanism where there is dissociation between pulse and temperature. This finding is important to recognize since it may provide further insights into the potential underlying causes of disease. There is no known proposed mechanism to explain this phenomenon. We hypothesize that relative bradycardia is the central mechanism reflecting and influenced potentially by the direct pathogenic effect on the sinoatrial node as well as cross-talk between the autonomic nervous system and immune system. Cardiac pacemaker cells may act as a target for inflammatory cytokines leading to alteration in heart rate dynamics or their responsiveness to neurotransmitters during systemic inflammation. These factors account for the important role of how the host response to infectious and non-infectious causes influences the appearance of relative bradycardia. We propose several methods that may be useful to confirm the proposed theoretical framework to further enhance our understanding of this paradoxical phenomenon. This includes measuring, during the episode of relative bradycardia, proinflammatory and anti-inflammatory cytokines, monitoring heart rate variability (HRV), and assessing underlying comorbidities and outcomes in patients with the same disease.

## Introduction

Typically in response to infectious (e.g. legionelliosis) and some non-infectious (e.g. drug fever) conditions the pulse rate increases by 10 beats/min for each Fahrenheit degree increase in body temperature from 101 °F (38.3 °C) corresponding to a heart rate of 110 beats/min [1]. Failure of this phenomenon to occur or the dissociation between increase temperature and pulse is referred to as pulse-temperature dissociation or Faget sign [2]. The term “relative bradycardia” is used to describe the paradoxical relationship between pulse and temperature or the failure of the pulse to rise when the temperature exceeds 102 °F [1]. To the best of our knowledge, there is no known unified mechanism to explain relative bradycardia.

Relative bradycardia has been most commonly described, although not exclusively seen, in infections caused by intracellular gram negative, non-enteric pathogens as well as certain viral and parasitic protozoan organisms. An intracellular pathogenetic effect does not appear to be sufficient by itself to explain relative bradycardia since it is also seen in patients with Leptospirosis, caused by the extracellular organism Leptospira, and is absent in Brucellosis, the intracellular gram-negative organism Brucella [1]. A variety of non-infectious causes for relative bradycardia have also been reported including lymphoma, factitious fever, drug fever, and central nervous system lesions; the mechanistic effect for this phenomenon has also not been previously accounted [1].

Relative bradycardia, regardless of its cause, is often poorly recognized, significantly underappreciated and underreported. The relative low prevalence of this sign may be due to the lack of a consistent case definition, lack of knowledge regarding its significance, timing of pulse and temperature recordings, and size of the studied population. When observed, this finding may provide important insights into the potential cause of disease. We postulate that HRV serves as a physiological predictor for relative bradycardia. Furthermore, we propose several potential pathways including autonomic nervous and immune mediated mechanisms that may account for the pathogenesis of relative bradycardia in non-physiological conditions.

## Heart rate variability

HRV is a viable physiologic marker to predict relative bradycardia. HRV reflects the continuous oscillation of the RR intervals (beat-to-beat interval) around its mean value. It differs from heart rate, which is a measure of the number of heartbeats as determined by ventricular contraction per minute. Both are primarily determined based on

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modulation of sinus node activity by sympathetic and parasympathetic autonomic nerves. HRV and heart rate reflect different concepts and thus high or low heart rate variability may be found in cases of high or low heart rate. In healthy subjects, for example, there is a fluctuation of the heart rate with respiration or respiratory sinus arrhythmia, increases during inspiration and decreases during expiration with high and low heart rate variability occurring respectively [3].

HRV is affected by a number of acute and chronic pathologic conditions including congestive heart failure (CHF), coronary artery disease (CAD), diabetes, systemic infection, or neurologic diseases [4–7]. For example, following a myocardial infarction, low heart rate variability is associated with higher mortality [8]. Similarly, reduced sympathetically mediated heart rate variability in children recovering from cardiac surgery has been shown to predict a fatal outcome [9]. Therefore, reduction in HRV, a manifestation of altered autonomic function under stress, is useful in predicting disease progression and prognosis [10]. The loss of normal HRV is associated with more severe diseases and worse prognosis [11], while increased HRV is associated with increased probability of successful resuscitation [12]. One study found that a drop in HRV occurs in 25% of patients prior to clinical diagnosis and treatment of sepsis signifying that increased cardiac vagal activity and decreased sympathetic modulation precedes septic shock [13].

The sinoatrial node (SAN) is the dominant pacemaker in the mammalian heart. Biological clocks are the internal mechanisms that orchestrate the periodicity of heart rate and rhythm. ATP is consumed to maintain the basal spontaneous action potential firing rate. Generation and utilization of ATP is modulated via neurotransmitter release from the parasympathetic and sympathetic nerves to the SAN [14]. We propose that relative bradycardia, found in patients with specific diseases is a paradoxical phenomenon representing cross-talk between the autonomic nervous system and the immune system. Cardiac pacemaker cells may act as a target for inflammatory cytokines leading to alteration in heart rate dynamics or their responsiveness to neurotransmitters during systemic inflammation.

## Proposed mechanism I

### *Autonomic nervous system*

We postulate that the disturbance in autonomic control of heart rate results from one or more of the following mechanisms including: 1) direct toxic effect of inflammatory factors upon peripheral nerves, 2) alterations in vasomotor activity within the central nervous system, and/or 3) impaired neuronal transmission to the heart or changes in end organ responsiveness caused by polyneuropathy.

Interestingly, the very notion of sympathetic versus parasympathetic activation has been challenged, suggesting that the reduction in HRV during sepsis is ascribed to uncoupling of the autonomic and cardiovascular systems and may be helpful in early identification of paradoxical bradycardia [15,16]. This is supported by evidence that vagally mediated pathogen-induced bradycardia is an extension of the cholinergic anti-inflammatory reflex. The rapid onset of bradycardia suggests that pathogens exert a direct effect early on the nervous system, activating vagal sensory neurons either peripherally or within the ganglia via the cytokines or receptors, and later indirectly through cytokines or other secondary mediators [17–19]. This explanation may account for the finding that relative bradycardia may occur early or later in the infection or during the early convalescent period as described in cases of leptospirosis and typhoid fever or signifies delayed fever defervescence in the case of Q-fever or scrub or murine typhus [20].

Both central and peripheral neurological mechanisms maybe responsible for relative bradycardia in diseases. It has been suggested that failure of the core mechanisms that support homeostatic responses to stress, arousal, and vegetative functions is related to brain dysfunction in patients with sepsis [21]. Some mechanisms proposed involve augmentation of sympathetic tone, by “decomplexification” or down-regulating physiologic signals [22]. Further direct evidence to support a central mechanism is that bilateral microinjection of the double-stranded kB decoy DNA into rostral ventrolateral medulla (RVLM) 24 h before lipopolysaccharide (LPS) treatment significantly reverses sepsis induced complications including hypotension, bradycardia, and the decrease in the power density of vasomotor components [23,24].

Additionally, HRV exhibits a circadian variation under normal conditions [25,26]. It has been demonstrated that stress induces alterations in the homeostatic dynamics of the feedback structures that creates “uncoupling of biologic oscillations” and disrupts these regulatory structures [27]. In the HRV spectra, the high-frequency (HF) component is linked to respiration and is mediated predominantly by cardiac vagal activity, whereas the low-frequency (LF) component is mediated by sympathetic, parasympathetic, and renin–angiotensin system activity occurring in sepsis [28]. Several studies documented impaired sympatho-vagal balance with a low LF/HF ratio in septic patients [29,30]. Imbalance between LF and HF ratio represents progressive crossing of these “tipping points” which would lead to cascading systems failure and the clinical syndrome of sepsis [31]. These factors account for the important role of how the host response to infectious and non-infectious causes influences the appearance of relative bradycardia.

## Proposed mechanism II

### *Immune system*

We postulate that the degree of alteration of consciousness is associated with the early occurrence of relative bradycardia and may be influenced by endotoxin/LPS and cytokines released by the pathogen and host respectively. Additionally, bacterial LPS have limited ability to pass the blood-brain barrier, so the central effects of LPS are likely mediated by cytokines. The immune response is affected by the activity of circulating immune cells including nature killer cells, T lymphocytes, and various inflammatory cytokines, influenced by input from parasympathetic and sympathetic systems, with cytokines modulating sympathetic and parasympathetic tone. For example, selective proinflammatory cytokines such as tumor necrosis factor (TNF) α, interleukin (IL)-1 and Il-6 may decrease vagal tone while conversely, stimulation of the afferent limb of the vagus nerve decreases levels of proinflammatory cytokines thereby modulating the host response to infection. Further support for this finding is based on the identification of elevated levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), Il-6 and TNF α in a patient with cyclic neutropenia presenting with relative bradycardia and periodic fever [32]. Upstream interactions leading to an accentuated vagal response is a proposed mechanism for the relative bradycardia observed in selected patients.

Many cytokines including IL-10, IL-6, IL-8, IL-5, IL-2, IL-1α, IL-17, IL-4, IL-18, TNF-α, and GM-CSF levels are significantly increased during infection [33–35]. Furthermore, their levels likely correlate with specific clinical manifestations and illness severity [36]. Activating innate immune cells and stimulating pathways linked to the production of inflammatory genes such as the mitogen-activated protein kinase (MAPK), nuclear factor kappa light chain enhancer of activated B cells (NF-κB) and Janus kinase-signal transducers and activators of transcription JAK-STAT signaling pathways [37], is reflected in decreased HRV [16]. Suppression of cytokine production with dexamethasone resulted in resolution of abnormal HRV, and is explained by its ability to inhibit LPS-induced elevations in serum TNF-α and IL-6 [38–40]. These findings provide further support of the relationship between cytokines, immune cells and stimulating inflammatory pathways and paradoxical bradycardia measured by HRV.

Herein, we proposed some of the most important central mediators potentially involved in relative bradycardia.