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# PHYSIOLOGICAL BASIS OF THE HEART

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**Annotation:** Heart rate variability can be an indicator of an individual cardiovascular condition. In this review, we will discuss the two primary rhythmic oscillations that underlie the complexity of the heart rate waveform. The first oscillation occurs over several cardiac cycles, is respiratory related, and termed respiratory sinus arrhythmia. The second oscillation occurs at an approximate 10 s cycle. Due to the closed-loop nature of the control system of cardiovascular oscillations, it is difficult to define specific relations among cardiovascular variables. In this review, we will present the feedforward and feedback mechanism that underlie both oscillations and their implication as quantitative measures of autonomic circulatory control. We will also review the various methodologies to assess them.

**Key words:** Cardiac chronotropy, Frequency domain, Time domain.

Background Variability in beat-by-beat heart period is an intrinsic characteristic of healthy cardiac functioning. This variability can reflect purposely generated responses to internal and external stimuli and may not reflect simple random fluctuations. For example, various stressors result in characteristic changes in variability and various disease states are associated with lesser variability. The primary regulators of cardiac chronotropy, the parasympathetic and sympathetic nervous systems, are key determinants of the magnitude of spontaneous cardiovascular variability. In this review, we will focus on two primary rhythmic oscillations occurring at the respiratory frequency and at the ~0.10 Hz frequency since these two have the greatest importance for human cardiovascular control. Moreover, these cardiovascular variabilities have been most studied and most often used to index autonomic circulatory control. Physiological basis Cardiac chronotropy can be represented in two ways. Representation of cardiac chronotropy by heart rate (HR) as beats per minute (bpm) has a long history because it is readily and easily accessible by simple palpation of an artery. However, HR provides an estimate that is normalized to time (i.e., 60 s). With the development of the electrocardiogram (ECG), physiologists were able to minutely assess the time interval between beats in milliseconds. In fact, this linear measure of cardiac chronotropy better reflects its autonomic regulators. The interval between R waves in the ECG (RRi) is most commonly used and reflects a linear relationship to both parasympathetic (vagal) and sympathetic stimulation [1, 2]. Given that HR is the inverse of RRi, fluctuations in the two do not always conform to one another (Fig. 1). Hence, heart rate variability should not be used as anything more than a misnomer and instead RRi variability should be used. In this review, out of convenience and convention, we will use the widely adopted term heart rate variability (HRV) to discuss the physiology and measurement of RRi variability. Fluctuations in heart rate are usually due to waxing and waning activity level in at least one arm of the autonomic nervous system (ANS). Under

normal conditions, the chronotropic state of the heart is entirely regulated by the sinoatrial (SA) node. The SA node is directly innervated by both parasympathetic (vagal) and sympathetic efferents. Although both vagal and sympathetic nerves exert opposite chronotropic action on the heart, these effects are not symmetrical [2–4]. Vagal effects have a distinctly shorter latency than sympathetic effects. Vagally mediated RRi lengthening is mediated by synaptic release of acetylcholine (ACh). The response is almost immediate due to the very short effect latency and high turnover rate of ACh, allowing the parasympathetic system to exert cardiac control on a beat-by-beat basis [5]. Sympathetically mediated RRi shortening is mediated by synaptic release of noradrenaline which is reabsorbed and metabolized relatively slowly [5]. This results in a delay between the onset of sympathetic stimulation and the resultant changes in cardiac control. Hence, the effect of sympathetic nerves on RRi encompasses longer delays and potentially longer effects than parasympathetic nerves. The characteristic delay and duration of the two autonomic arms result in different potential effects on HRV. That is, the faster vagal effects have the potential to act across a wide range of frequencies, from a single beat to many beats, whereas the sympathetic system may not. However, time domain quantification of HRV cannot discriminate frequency-specific effects. These can only provide global indexes for HRV. Frequency domain analysis can assess HRV across frequency components while ignoring random, non-rhythmic noise. While time domain is simple and global, the frequency domain eliminates noise and allows for easy differentiation of the two primary rhythmic oscillations contained in HRV. Hence, spectral analysis of HRV is the most precise and most widely used technique to assess specific rhythms that exist in the HRV. The majority of the data discussed below derives from frequency domain information. Respiratory frequency oscillations Respiratory sinus arrhythmia (RSA) is a rhythmic heart rate oscillation at the respiratory frequency and can be quantitatively measured as a high-frequency component (usually >0.15 Hz) in the power spectrum of RRi. RSA is a widely studied physiological phenomenon that reflects numerous cardiorespiratory interactions. RSA is typically characterized by RRi shortening with inspiration and lengthening with expiration. The magnitude of RSA is thought to reflect the degree of respiratory modulation of vagal outflow and arises from complex interactions of both central and peripheral factors. One possible driving mechanism for RSA is the response of RRi to arterial pressure fluctuations. During breathing, changes in intrathoracic pressure rhythmically alter venous return to the heart, thereby impacting cardiac output and subsequently changing arterial blood pressure. These arterial pressure changes engage the arterial baroreflex, generating oscillations in afferent activity to appropriately increase and decrease cardiac autonomic outflow, generating RSA. Indeed, in humans, respiration frequency and depth can strongly determine fluctuation amplitude [6–8]. The magnitude of RSA increases with increased tidal volume and decreased breathing frequency. It has been suggested that the magnitude of RSA might be due to respiratory changes in systolic blood pressure due to tidal volume and breathing frequency. Hence, it has been hypothesized that RSA represents baroreflex buffering of arterial blood pressure fluctuations induced by the mechanical effects of breathing. If that were the case, eliminating RRi fluctuations, and hence RSA, should result in increased respiratory related arterial pressure fluctuations. However, in young individuals, elimination of RSA via complete autonomic blockade decreased arterial pressure fluctuations in the supine position, and it increased them in only the upright position [9]. These findings are further supported by elimination of RSA through fixed-rate atrial pacing. Atrial pacing decreased respiratory-related arterial pressure oscillations in the supine position, but increased them in the upright position (Fig. 2) [10]. In addition, it is apparent that RSA does not subserve a role in stabilizing diastolic pressure in supine humans. Progressive increases and decreases of RSA via low doses of the parasympatholytic agent atropine results in parallel and proportional increases and decreases in diastolic pressure oscillations at the respiratory frequency [11]. Hence, it seems that RSA contributes to arterial

pressure oscillations in supine humans. Moreover, the postural differences can be explained by the shift in the phase relationship between RRi and systolic pressure oscillations. In the supine position, RRi oscillations are in phase with those in arterial pressure, but in the upright position, RRi oscillations follow those in arterial pressure [12]. This suggests that the arterial baroreflex is one important mechanism underlying RSA in upright but not supine humans. This could be due to the large caudal shift in blood volume consequent to assuming the upright posture that requires active and persistent baroreflex engagement to control arterial pressure [13]. However, baroreflex engagement does not explain the presence of RSA in supine humans. It is known that gating of excitatory input to the vagal cardiomotor neurons (CVM) partially contributes to RSA [14–16]. Data from animal models show CVM activity linked to the central respiratory cycle. While CVM activity in rats is greatest during inspiration [17], in cats, dogs, and humans, CVM are inhibited during inspiration and are mildly activated during expiration by stimulation of the arterial chemoreceptors and baroreceptors [18–20]. Thus, the susceptibility of CVM varies systematically during the respiratory cycle, and it is possible that RSA could arise from an efferent vagal oscillation that contributes to arterial pressure fluctuations by gating the excitatory input to the vagal motor neurons [3, 21]. The neural networks generating respiratory activity could not only drive respiratory motor neurons, but also impose patterns of activity in the vagal and sympathetic outflows. Functionally, this may provide a mechanism for the integration of cardiovascular and respiratory control [20]. Respiratory sinus arrhythmia is frequently used as an index of cardiac vagal tone or is even believed to be a direct measure of vagal tone. Substantial published data suggests that RSA quantifies tonic cardiac vagal activity [2, 22–26]. Despite physiological studies questioning respiratory sinus arrhythmia as a valid and reliable cardiac parasympathetic index [4, 27], numerous clinicians and experimentalists routinely estimate vagus nerve traffic to the heart with measurements of RSA. However, even though vagal outflow is the key contributor to HRV, there are significant caveats regarding the assumption that RSA is mediated exclusively by vagal mechanisms. Observations that β-blockers augment RSA have been interpreted as indicating a central vagomimetic effect for these drugs [28, 29]. However, the data may actually suggest that sympathetic activity opposes vagally mediated RRi oscillations. This would mean that differences in RSA could not solely be ascribed to differences in vagal outflow. For example, β-adrenergic blocking drugs that do and do not cross the blood-brain barrier equally result in increased RSA [30]. Moreover, enhancement of RRi oscillations via cardioselective β-adrenergic blockade is exerted across a wide range of frequencies, from very low to high breathing frequencies [31]. If the delay and duration of sympathetic nervous effects constrain their impact to lower frequencies may not linearly reflect the vagally mediated chronotropic response and challenge the assumption that RSA is always a purely vagal mechanism.

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