The rhythm of the heart has not only fascinated cardiologists but also inspired poets and musicians. Indeed, the periodic beat of the heart was used to define the speed of music. In music notation, the traditional Italian term “moderato” originally referred to one beat of the measure per walking pace (76–80 paces/min) or heartbeat (~72 beats/min). The use of the heartbeat to define the speed of music may imply that the periodicity of the beat of the heart is very constant. However, this is not necessarily the case. In fact, loss of heart rate variability can indicate severe cardiovascular diseases and reliably predict poor outcome of such conditions (18, 22, 27, 47a). This In Focus article reviews sources of heart rate variability, its role as a prognostic marker for cardiovascular diseases, and its application in estimation of cardiac autonomic nervous system activity. All of these topics have been addressed intensely in articles published in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology during the last two years.

In healthy subjects, the sinoatrial node located at the posterior wall of the right atrium initiates each beat of the heart. Due to the unstable membrane potential of the myocytes located in this region, action potentials are generated periodically at a fairly constant frequency. This relatively constant frequency generated by the autorhythmicity of the sinoatrial node is modulated by many factors that add variability to the heart rate signal at different frequencies. According to the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (47a) these frequencies are classified into 1) ultra-low frequencies (ULF; >5-h cycle length) that include the circadian rhythm (6, 9, 34, 54); 2) very low frequencies (VLF; >25-s cycle length) that are supposed to be affected by temperature regulation (1, 7, 34, 52, 54) and humoral systems (9, 36); 3) low frequencies (LF; >6-s cycle length in humans) that are sensitive to changes in cardiac sympathetic (and presumably parasympathetic) nerve activity (27, 30); and 4) high frequencies (HF; 2.5- to 6.0-s cycle length in humans) that are synchronized to the respiratory rhythm (5) and are primarily modulated by cardiac parasympathetic innervation (38).

The most prominent oscillation in the ULF band of the heart rate spectrum is the circadian rhythm. The autonomic nervous system contributes significantly to circadian heart rate variability. Using long-term recordings in conscious rabbits, Barrett et al. (6) demonstrated a strong circadian rhythm in heart rate, mean arterial blood pressure, renal blood flow, and renal sympathetic nerve activity. The importance of this study is that it clearly demonstrates that sympathetic nerve discharges exhibit a strong circadian rhythmicity. The paraventricular nucleus of the hypothalamus (PVN) appears to play a central role in mediating the circadian rhythm of autonomic nervous system activity. First, GABAergic and glutamatergic neurons project from the suprachiasmatic nuclei of the hypothalamus (SCN) to spinal-projecting neurons of the PVN (12). The SCN is the major central oscillator that triggers the day/night cycle. It receives photic input from the retina (47) and drives many neuroendocrine, metabolic, autonomic, and behavioral circadian rhythms (14, 16, 21, 31, 35, 44, 46, 50). In addition, microinjections of the inhibitory neurotransmitter GABA into the PVN of anesthetized rats elicit dose-dependent decreases in renal sympathetic nerve activity, whereas bicuculline (a GABA antagonist) increases renal sympathetic nerve activity (56). Second, from the PVN, neurons project to the nucleus of the solitary tract (that integrates inputs from the baroreceptors), the nucleus ambiguus (origin of preganglionic parasympathetic neurons to the heart), the rostroventrolateral medulla (location of sympathetic premotor neurons), and the intermediolateral cell column of the thoracolumbar spinal cord (location of preganglionic sympathetic neurons). Thus PVN neurons can modulate autonomic nervous system activity by sending inputs to major sites of autonomic nervous system regulation. As an example, a pivotal role of the PVN for sympathoexcitation during parturition was recently demonstrated in sheep. The increase in sympathetic nerve activity that accompanies birth in maternal animals was prevented by stereotactic lesioning of the PVN (43). Taken together, a major component of the circadian heart rate variability is elicited by diurnal fluctuations in autonomic nervous system activity, generated by corresponding fluctuations of neuronal activity within the PVN, which depend on circadian inputs originating from the SCN.

It has been suggested that thermoregulation affects VLF heart rate variability (10, 26). Cooling the heart causes bradycardia, a mechanism used in heart surgeries. Conversely, fever is known to increase heart rate. Raising body core temperature from 36.0 to 36.6°C caused an increase in heart rate by almost 40 beats/min in male subjects (1), whereas acutely reducing ambient temperature from thermoneutral conditions (35°C) to 29, 23, and 17°C, reduced heart rate from 400 to 250 beats/min in 8-day-old rats (7). In addition, lowering temperature in the isolated working...
rat heart from 37 to 31°C reduced heart rate from 332 to 215 beats/min and markedly increased heart rate variability (28), indicating that parts of the temperature effects on heart rate and heart rate variability are independent from the autonomic nervous system. In contrast to the tachycardia that accompanies acute elevations in temperature, chronically raising ambient temperature in adult rodents from a standard housing temperature of 21–23°C to thermoneutral conditions (29–30°C) reduced heart rate by roughly 50 beats/min in rats (34) and by 200–300 beats/min in mice (54). The authors of these articles (34, 54) suggested that standard housing temperatures are associated with cold stress that causes parallel activation of brown adipose tissue, cardiac, and vasomotor sympathetic drives that elicits nonshivering thermogenesis and tonically elevates heart rate and arterial blood pressure. These and other studies indicate that both direct effects of temperature on pacemaker activity of the sinus node (28) and indirect effects mediated via the autonomic nervous system (11, 25, 51, 55) mediate temperature effects on heart rate and heart rate variability. Thus fluctuation in temperature is an important source of heart rate variability that should not be underestimated. In a more recent study, this was taken into account by core body temperature correction of heart rate variability (3).

Endocrine factors affecting heart rate variability include thyroxine, reproductive hormones, the renin-angiotensin system, steroids, and others. Chronic subcutaneous infusion of angiotensin II in rats markedly increased blood pressure and heart rate variability, expressed as standard deviation (9). In contrast, chronic corticosterone treatment is likely to reduce baroreflex-mediated heart rate variability, because baroreceptor-heart rate (39) and baroreceptor-renal sympathetic nerve activity reflex sensitivity (41) were blunted in chronically corticosterone-treated rats. Furthermore, an interaction between angiotensin II and glucocorticoids was recently described. Intracerebroventricular microinjections of angiotensin II AT1 receptor antagonists caused marked decreases in mean blood pressure and heart rate in rats chronically treated with corticosterone but not in control animals (40). This interaction is likely to take place in the central nervous system, because peripheral angiotensin II AT1 receptor blockade did not alter the effects of betamethasone treatment on blood pressure, heart rate, and baroreceptor-heart rate reflex sensitivity in newborn lambs (42).

Adenosine is a substance less known to affect heart rate variability. It is produced locally in the heart (53) and binds to A1-adenosinergic receptors, which are among the earliest expressed G protein-coupled receptors in the heart (36). The A1-adenosinergic agonist N8-cyclopentyladenosine dose-dependently reduced heart rate in murine embryos, whereas 1,3-dipropyl-8-cyclopentylxanthine, an A1-adenosinergic antagonist, increased heart rate (36). Adenosine also exerts central nervous system effects in various brain areas (15, 20). Microinjections of adenosine into the nucleus of the solitary tract of awake rats caused dose-dependent changes in heart rate: low doses (0.01 nmol) produced a bradycardic response, whereas high doses (2.5–5.0 nmol) elicited a tachycardic response (15). Thus adenosine may indeed be involved in the regulation of heart rate and modulate heart rate variability via local cardiac and central nervous system effects.

It has been proposed that the intrinsic cardiac nervous system plays an active role in regulating cardiac function (4, 37, 45, 57). This nervous system consists of sympathetic and parasympathetic neurons and interconnecting local circuits (37). Neurons in the canine right atrial ganglionated plexus (RAGP) spontaneously generate activity even after chronic cardiac autonomic denervation (45). Right atrial neurons in patients undergoing coronary artery bypass surgery generated spontaneous activity that was unrelated to the cardiac cycle but sensitive to changes in systemic arterial pressure, indicating that these neurons receive pressure-sensitive sensory inputs (4). In addition, it has been suggested that substance P acts as a neuromodulator and neurotransmitter in intracardiac ganglia of the guinea pig, modulates the response to vagal inputs, and triggers action potentials at the site of parasympathetic ganglia independent of acetylcholine (57). Furthermore, the right atrial (RAGP) and the posterior atrial ganglionated plexus (PAGP) appear to have different functions. Ablation of the PAGP reduced vagally mediated bradycardia by 26%, whereas RAGP ablation completely abolished this response. Inhibition of sympathetically mediated tachycardia by vagal stimulation was attenuated by ablation of either plexus (37). Thus parasympathetic efferent neurons are primarily located in the RAGP, whereas prejunctional parasympathetic-sympathetic interactions also involve neurons within the PAGP (37). The spontaneous activity of neurons in the intrinsic cardiac nervous system, even after cardiac denervation (45), suggests an active role of this system in regulating heart rate. However, the impact of the intrinsic cardiac nervous system on heart rate variability remains to be elucidated.

The importance of the autonomic nervous system for heart rate variability in humans becomes apparent in patients following cardiac transplantation, in whom heart rate variability is markedly reduced (49). Although reinnervation is possible after months and years, initially transplanted hearts can be considered to be denervated. Thus the reduced heart rate variability in cardiac transplanted patients (49) underlines the importance of an intact autonomic innervation for spontaneously occurring heart rate variability. A major component of the chronotropic effect of the autonomic nervous system is linked to cAMP. Intracellular cAMP increases the inward current of Na+ (funny current, If), which determines the rate of the slow diastolic depolarization that precedes each action potential. The activity of adenylate cyclase and thus intracellular cAMP levels are increased by stimulation of sympathetic β1-adrenergic receptors and decreased (via a G1 protein) by stimulation of parasympathetic muscarinic receptors. Thus cardiac sympathetic inner-
vation increases the rate of the slow diastolic depolarization and accelerates heart rate, while cardiac parasympathetic innervation elicits opposite effects. Interestingly, parasympathetic-mediated changes in heart rate occur much faster than sympathetic-mediated effects on heart rate (27, 30, 47a). As a result, cardiac sympathetic nervous system activity can only affect LF components of heart rate variability, whereas the parasympathetic nervous system can also modulate HF components. A hitherto unsolved question in this context is if the rapid heart rate response to parasympathetic stimulation compared with the slow effect of sympathetic inputs is due to 1) different kinetics of β1-adrenergic vs. muscarinic receptors, 2) different kinetics of adenylate cyclase vs. phosphodiesterase, the enzyme that cleaves cAMP, or 3) fast parasympathetic-mediated opening of K_ACh channels (via muscarinic receptors and a G_K protein). Support for the latter possibility comes from experiments in the rabbit sinoatrial node that demonstrated that activation of K_ACh channels contributes to the initial slowing of heart rate as a result of vagal stimulation (8).

On the basis of the different frequency response characteristics of sympathetic and parasympathetic modulation of heart rate, frequency analysis of heart rate variability is often used as a tool to determine “autonomic balance” or sympathetic and parasympathetic nervous system activity (27, 47a). As an example, the wavelet transform was recently used to determine cardiac autonomic responses to reperfusion in patients with thrombolysis after coronary thrombosis. Depending on the location of the infarct, marked alterations in LF or HF spectral power of heart rate or in the LF/HF ratio was observed in all successful reperusions (48).

The HF component corresponds to the frequency of respiration and is driven by the vagus as indicated by the strong respiratory pattern of cardiac vagal motoneurons in the nucleus ambiguus (38). The LF component has been ascribed to sympathetic modulation of cardiac pacemaker activity, because a variety of studies demonstrated that acute interventions that increase sympathetic nervous system activity, such as orthostatic perturbations (17, 19, 33), mental stress (32), or handgrip exercise (13, 24) increases LF spectral power of heart rate (27, 30). In addition to acute perturbations of cardiac sympathetic nerve activity, feedback oscillations generated by the baroreceptor reflex also appear to contribute to LF spectral power of heart rate as it was demonstrated that sinoaortic denervation markedly reduces the LF component (27, 30). Despite the strong modulation of heart rate by the autonomic nervous system, the LF and HF spectral components of heart rate variability may not always be reliable markers for cardiac sympathetic and parasympathetic “tone” (30). In a recent study, muscle sympathetic nerve activity was recorded together with heart rate variability during application of lower body negative pressure that is known to increase muscle sympathetic nerve activity (17, 33). At higher levels of lower body negative pressure (~15 mmHg), both muscle sympathetic nerve activity and relative LF spectral power of heart rate increased significantly, whereas HF spectral power decreased (17). These findings suggest that LF spectral power reflects cardiac sympathetic “tone.” However, no correlation within subjects was found between changes in LF/HF ratio and muscle sympathetic nerve activity (17). Thus heart rate variability does not reliably reflect the sympathetic response to orthostatic stress.

Respiration-related fluctuation of heart rate (respiratory sinus arrhythmia) is probably the most often investigated component of heart rate variability, as it is believed that this component reflects respiration-driven vagal modulation of sinus arrhythmia (27). In a recent study, Rentero et al. (38) recorded the electrical activity from cardiac vagal motoneurons in the nucleus ambiguus. Firing of these neurons was modulated by the central respiratory cycle. This and other studies support the view that respiratory sinus arrhythmia is generated by central coupling of the respiratory oscillator with autonomic centers in the brain stem. However, a mechanical cardiopulmonary coupling as a source of respiration-related heart rate variability has also been suggested (5). The Bainbridge reflex causes a tachycardia in response to hypervolemia. This reflex is initiated by atrial mechanoreceptors and uses efferent sympathetic and parasympathetic pathways to modulate heart rate in response to changes in central venous pressure (23). Thus respiratory changes in central blood volume cause corresponding respiratory fluctuations in cardiac autonomic nervous system activity via the Bainbridge reflex. Only the parasympathetic component of the efferent pathway of the reflex can contribute to respiratory sinus arrhythmia, because sympathetic actions on heart rate are too damped to follow the respiratory frequency. The gain and phase of the transfer function between respiratory changes in lung volume and R-R intervals of the ECG were calculated in human subjects during graded changes in central blood volume (5). At the respiratory frequency, the phase was ~180 degree, indicating that an inspiratory increase in central blood volume was associated with a decrease in R-R interval (increase in heart rate). Furthermore, the gain of the transfer function at the respiratory frequency steadily increased with increasing central volumes (except at the highest volume). Both of these findings confirm the presence of the Bainbridge reflex in humans (5). Thus, in addition to the central coupling of respiratory oscillators with cardiovascular centers, the Bainbridge reflex may contribute to respiration-related heart rate variability by mechanical cardiopulmonary coupling.

There is general agreement that low heart rate variability is an unfavorable prognostic marker for cardiovascular diseases, such as diabetic autonomic neuropathy, hypertension, myocardial infarction, and heart failure (18, 22, 27, 29, 47a). Heart rate variability (variance of R-R intervals) was reduced in patients with mild hypertension (29) compared with normal values (1,134 ± 202 vs. 3,466 ± 1,018 ms²) provided by the Task Force (47a). In the rat model of myocardial
infarction-induced congestive heart failure, Francis and colleagues (18) reported loss of spontaneous heart rate variability 6 wk after coronary artery ligation. Interestingly, reduced heart rate variability was also observed in a rat model of depression that is based on chronic (4 wk) mild stress application (22). Because depression is an independent risk factor for coronary artery disease, this finding may realistically model a human disease process. The reduction in heart rate variability was abolished by β-adrenergic receptor blockade, indicating that the reduced heart rate variability in this model of depression is related to elevated cardiac sympathetic tone (22).

In summary, heart rate variability is generated by multiple factors not exclusively limited to the autonomic nervous system. Specific frequency components of heart rate variability mirror acute perturbations of the autonomic nervous system but do not always reflect autonomic nervous system activity. Simple statistics of heart rate variability, such as the standard deviation of R-R intervals in the ECG, can reliably predict the prognosis of cardiovascular diseases.

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REFERENCES


