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by [Kristal-Boneh E](#), [Raifel M](#), [Froom P](#), [Ribak J](#)

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Heart rate variability in health and disease

by Estela Kristal-Boneh, PhD,¹ Mark Raifel, BSc,¹ Paul Froom, MD,^{1,2} Joseph Ribak, MD^{1,2}

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Beat-to-beat fluctuations in heart rate (HR) or instantaneous HR is mainly determined by activity of the cardiac sympathetic and parasympathetic systems. Despite the need for standardization in methodology to facilitate the interpretation and comparison of results, the data presented in this review clearly show that there are individual differences in heart rate variability (HRV) and that these differences partly reflect differences in the degree of parasympathetic and sympathetic stimulation of the heart. HRV and its spectral components can be easily and noninvasively assessed and can provide valuable information to the occupational physician. Measurements of HRV and the quantification of its spectral components are powerful predictors of cardiovascular morbidity and mortality. Therefore it may help assess the return to work of patients with ischemic heart disease. Studies in the workplace can also indicate the effects of various stresses of the work environment on such patients and even on asymptomatic workers.

Key words occupation, review.

For a long time the study of heart rate variability (HRV) was confined to the laboratory. However, thanks to recent advances in microprocessor technology, the analysis of beat-to-beat variation has become possible also to the clinician. The increasing number of HRV investigations in the clinical and physiological literature emphasizes the value of HRV measures as a prognostic tool for the rapid and noninvasive assessment of the autonomic nervous function of the heart. Provided herein is an update of the current knowledge on HRV, in health and disease.

Heart rate variability — definition and causes

HRV is defined as spontaneous fluctuations in sinus rate due to internal and external body processes. It is usually measured as the standard (or average) deviation from the mean R-R intervals of all cardiac cycle lengths (R-R intervals for normal sinus beats) over a given period, most commonly 5 min. Beat-to-beat fluctuations in heart rate are mainly determined by the activity of the cardiac sympathetic and parasympathetic systems. Physiological experiments have demonstrated a correlation between cardiac nervous activity and immediate R-R interval

changes (1—4). These studies form the basis for the examination of autonomic cardiac activity by HRV. The rate and variation of heart beats are the result of a complex interaction between sympathetic and parasympathetic efferent impulse activity in addition to the influence of sinus node pacemaker properties (5—7). The sinoatrial (S-A) node is directly and richly innervated by both sympathetic and parasympathetic (vagus) nerve fibers, which are continually active; the atrioventricular (A-V) node is less affected. Parasympathetic stimulation hyperpolarizes the S-A node, decreasing the rate of spontaneous firing and the cardiac rate. Sympathetic nerve endings, on the other hand, release norepinephrine, and the adrenal medulla releases epinephrine, stimulating the spontaneous firing rate of the S-A node and increasing cardiac rates. Due to the high turnover of acetylcholine, the S-A node responds faster to parasympathetic than sympathetic stimulation, enabling beat-to-beat parasympathetic regulation. The respiratory cycle has a major effect on the heart rate. The variation in blood pressure during each cycle of respiration stimulates and inhibits the baroreceptor alternately, causing a reflexive slowing and speeding up of the heart. During each respiratory cycle, the negative intrapleural pressure increases and decreases and therefore leads to changes in the effective pressure in the veins of the chest. This process elicits a

¹ Occupational Health & Rehabilitation Institute, Raanana, Israel.

² Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

waxing and waning Bainbridge reflex and leads to a variable cardiac rate. Furthermore, the respiratory center of the medulla is excited during each respiratory cycle, and some of the impulses "slip over" from the respiratory center into the vasomotor center, causing an alternating increase and decrease in the number of impulses transmitted to the heart through the sympathetic and vagus nerves. There are however other factors which influence sinus rhythm, including a series of feedback loops which strive to maintain a homeostatic condition within the body: tonic and phasic baroreceptor and chemoreceptor reflexes, thermoregulatory and blood pressure control reflexes, and vasomotor reflexes.

Indices of heart rate variability

Originally, HRV was assessed manually from calculations of the mean R-R interval and its standard deviation measured on short-term electrocardiograms (figure 1). Recently, however, the advances in recording techniques, the availability of increased computing power, and innovative microprocessor technology have enabled the analysis of long-term records. Autonomic function during the day and night (8–10) can now be assessed by measuring HRV on 24-h Holter recordings. This is important since HRV undergoes circadian changes similar to the heart rate to which it has been shown to be inversely correlated (10, 11). In fact Rich et al (11) found that a reduced 5-min HRV span was correlated only with mortality; however, when HRV was computed over the entire 24-h span, it correlated also with other Holter variables (10). It is important, therefore, when studies are compared, to specify the time period over which HRV was assessed.

Figure 1. Normal R-R intervals from an electrocardiogram.

There are various indices of HRV measures available; Opmeer (12) reported finding 26 different measures in the literature. Kleiger et al (10) used the standard deviation of all R-R intervals over 24 h, whereas Magid et al (13) used the mean of the standard deviations of the R-R intervals obtained from successive 5-min periods over 24-h. Others measured the standard deviations of the normal mean R-R interval obtained from successive 5-min periods over 24-h, called the SDANN index (14). This measure basically shows how much the heart rate differs during each 5-min period from the overall day-long mean heart rate. Yet others have used the SD index, that is, the mean of the standard deviations computed for each successive 5-min period over 24-h (15), a measure of the variation that occurs within 5-min periods rather than the variation that occurs over longer time intervals; the pNN50 index — instances per hour in which two consecutive normal R-R intervals differ by more than 50 ms over 24-h (8); the base of the triangular area under the main peak of the R-R interval frequency distribution diagram obtained from 24-h recording (16); or the rMSSD index, the root-mean square of the difference of successive R-R intervals.

Spectral analysis of heart rate variability

Although it is generally accepted that the various methods measuring peak-to-peak variation in cardiac cycle lengths can be used as an index of parasympathetic activity (3, 8), information on the changes in both sympathetic and parasympathetic activity of the heart may be obtained only by using spectral analysis. The peak-to-peak variation is usually represented as a tachogram (figure 2) in which the y-axis is the time between beats and the x-axis is the number of beats. It may also be represented as a sequence of impulses, with unit amplitude on the y-axis and time on the x-axis, which synchronize

Figure 2. Tachogram. The y-axis is the time between beats and the x-axis is the number of beats.

with the QRS complexes of the electrocardiogram (17). Both methods basically measure a random signal. Spectral analysis of the HRV provides information on the different statistical components of the signal (18). It transforms the signal from time to frequency on the x-axis (19) by representing it as a combination of sine and cosine waves, with different amplitudes and frequencies, which are used to describe its spectral components. This is the classic nonparametric approach for determining rhythmic components and is known as the Fourier transform (FT) (20).

The HRV spectrum (figure 3) contains two major components. The first is a high-frequency (0.18–0.4 Hz) component which is known to be synchronous with respiration and has been considered a quantitative evaluation of respiratory sinus arrhythmia (RSA) (21). The RSA is mediated solely by the vagus nerve (21–26). Because it disappears after atropine, its magnitude may represent a clinically useful index of vagal activity (21). The second is a low-frequency (0.04 to 0.15 Hz) component that can be altered by interventions that functionally increase or pharmacologically block the sympathetic drive to the heart. Thus the low-frequency component is mediated by both the vagus and the cardiac sympathetic nerves, and its activity reflects sympathetic activity with vagal modulation (21, 24, 27).

The power of spectral components is the area below the relevant frequencies, presented in absolute units (square milliseconds) (figure 3). According to Parseval's theorem, the total power of a signal, integrated over all frequencies, is equal to the variance of the entire signal. The total power of the R-R interval spectrum within a given frequency band is therefore a measure of the amount of total R-R interval variance contributed by fluctuations within that frequency range. The power of a relevant frequency band may also be given as the percentage of the total spectrum power, which is a convenient way to quantify the magnitude of each relevant spectral component. Accordingly, a low-to-high frequency ratio could be a useful index of the parasympathetic-sympathetic balance (28, 29). Although only low- and high-frequency components are widely accepted as measures of sympathetic and parasympathetic heart modulation (24, 28, 30–35), there is an ultralow-frequency component (< 0.03 Hz) that may represent humoral and thermoregulatory factors (36). However, since very slow rhythms are correctly assessed only over long periods (hours), this component is not always analyzed (35).

To obtain a correct spectral analysis (and, by definition, a correct FT), the signal must show some characteristics of stationarity; that is, its statistical properties must not change over time. Clearly no "real-life" signal possesses stationary properties in the strict sense. In practical applications, the most that can be hoped for is that the signal does not depart "too far" from stationarity over the

Figure 3. Power spectrum of heart rate variability. (PSD = power spectral density)

observed time interval (37). This is the reason for using different methods for time-variant spectrum estimation. The correct estimation can be obtained by dividing the nonstationary signal into quasistationary overlapping segments. Thus the analysis by means of FT is generally limited to temporal windows a few minutes long, containing 265–512 consecutive heart cycles. During such time intervals, the variability signals are supposed to maintain a certain level of stationarity under normal conditions, if no external or internal perturbations are present (38, 39). Alternatively, one can assume that the time series is the output of a given mathematical model with the spectrum calculated as a function of model parameters (40–42). The relative advantages of the various methods of spectral analysis are unclear and deserve further study.

Heart rate variability in health and disease

A high degree of HRV is found in healthy subjects with normal hearts (43). However, several physiological and disease states produce alterations in autonomic function which attenuate the change in heart rate occurring both at rest and under stress (44–49).

Age

Although resting heart rate does not change significantly with increasing age, there is a decrease in HRV (21), which may be therefore a biological marker of the aging process. The effect of age on HRV has been attributed to a decline in efferent vagal cardiac tone and decreased beta-adrenergic responsiveness (8, 9, 24, 50). Autonomic derailments have also been reported to augment cardiovascular degeneration in the aging population, shifting the autonomic balance toward sympathetic dominance (51–53).

Exercise

Sinus arrhythmia may be marked in conditioned athletes and has been generally regarded as indicative of cardiovascular fitness (9, 54). Recent exercise training studies have revealed significant elevations in HRV after significant improvements in aerobic capacity (55—57). De Meersman (57) found that habitual aerobic exercise appears to play a role in the maintenance of augmented HRV in active men when compared with age- and weight-matched sedentary referents. This phenomenon suggests the beneficial role of long-term aerobic exercise in mitigating the age-dependent loss of HRV in physically active persons. The mechanisms responsible for increasing HRV are unclear, although there is some evidence that low-pressure cardiopulmonary and high pressure baroreceptor reflexes are involved (58—60).

Coronary artery disease

Low HRV can be found in patients with severe coronary artery disease and congestive heart failure (8, 43, 61). Several lines of evidence indicate that low HRV may be associated with increased cardiovascular disease-related morbidity and mortality. Decreased HRV has been found to be a potent predictor of cardiac mortality after acute myocardial infarction, independent of ventricular function, ventricular ectopic activity, heart rate, and other previously identified prognostic indicators (10, 62—68). Bigger et al (69) found that power spectral measures of HRV were predictors of all-cause, cardiac, and arrhythmic mortality and sudden death. Patients with low values were two to four times more likely to die over an average follow-up of 31 months as were patients with high values. Patients after myocardial infarction with low HRV (< 50 ms), defined as the standard deviation of all normal R-R intervals over 24 h, had a 5.3 times higher relative risk of death than patients with the HRV of > 50 ms (67). Others have confirmed the increased risk of sudden death for subjects with lower HRV (70, 71). Odemuyiwa et al (72) compared HRV and left ventricular ejection fraction for the prediction of all-cause mortality, arrhythmic events, and sudden death in 385 survivors of acute myocardial infarction. They found that HRV is a better predictor of important postinfarction arrhythmic complications than left ventricular ejection fraction, but both indices perform equally well in predicting all-cause mortality. Decreased HRV has also been found to be an independent predictor of mortality in the 12 months following elective coronary angiography in patients without recent myocardial infarction (11). Recent clinical studies have found that low total HRV and low measures of various frequency domain components of HRV can identify patients who are at increased risk of arrhythmic events, especially after myocardial infarction (10, 14, 71,

73, 74). The decrease in HRV due predominantly to a reduction in underlying vagal tone (11, 24, 28, 34, 43, 48, 49, 75—80) may be either a direct or indirect result of coronary artery disease. Decreased vagal activity may result from damage to intrinsic cardiac nerves (denervation or stimulation of mechanosensitive and chemosensitive nerve endings) by myocardial ischemia or infarction (81—85) or may reflect increased sympathetic activity or decreased parasympathetic activity as a result of impaired left ventricular function (28, 86). An increased sympathetic efferent tone may be a manifestation of a prevailing excitatory sympathetic reflex elicited by sustained activation of sympathetic cardiac afferent fibers stemming from an abnormal mechanical or chemical stimulus located in the heart. In addition, changes in the sympathovagal balance may reflect a reduction in baroreceptor mechanisms or may be the result of a change in what is generally referred to as "central command" with a consequent increase in the sympathetic discharge. It is possible, however, that a decreased vagal activity may be involved in the cause of coronary artery disease rather than being the result of heart damage due to coronary artery disease (87). Hayano et al (87) studied patients referred for coronary angiography and found that the decrease in HRV was related only to the number of major coronary arteries with significant stenosis regardless of a history of myocardial infarction or a decrease in left ventricular function. A further study showed that the correlation with HRV was higher with the extent of coronary atheromatosis rather than the degree of coronary stenosis (88).

The mechanism underlying the increased mortality among patients with low HRV is not known. It has been suggested that alterations in cardiac autonomic tone, reflected in aberrant HRV, could predispose patients to the development of lethal arrhythmias (89, 90). In experimental studies, attenuation of vagal activity predisposed subjects to malignant ventricular arrhythmias (91—94), while vagal stimulation was found to be protective (95, 96). Huikuri and his co-workers (74) studied the temporal relation between change in HRV and onset of spontaneous episodes of ventricular tachycardia in patients at high risk of life-threatening arrhythmias. They found that all power spectral components of HRV were significantly lower before the onset of sustained ventricular tachycardia (VT) episodes than before the nonsustained VT runs. In contrast, HRV tended to increase before the onset of nonsustained VT runs compared with the 24-h average HRV. Fluctuations in HRV at the onset of VT episodes may, therefore, reflect changes in factors that can lead to electrical instability and facilitate the initiation or perpetuation of arrhythmias. It is known that an abnormal ventricular repolarization duration may be associated with an increased propensity for fatal arrhythmias (97). Merri and his co-workers (98) found that, in

normal persons, the autonomic nervous system directly influences ventricular repolarization duration (acting in the ventricle). The interaction between abnormal regulatory events (7, 99) and arrhythmias appears to be a major pathophysiological determinant of sudden death in the early period after an acute myocardial infarction.

HRV is also associated with known risk factors for coronary artery disease. Kupari et al (100) studied the effects of risk factors of coronary artery disease on short-term HRV and found independent inverse relations between short-term HRV and low-density lipoprotein (LDL) cholesterol and between the total R-R interval power and LDL cholesterol and smoking, and a direct relation to alcohol use among women. These findings may partially explain the HRV impairment in chronic coronary artery disease. The association of smoking with a reduction in HRV has been reported consistently (9, 34, 87, 101).

Mitral valve disease

In a 9.2-year follow-up study of 38 patients with chronic severe mitral regurgitation from nonischemic causes (102), a low HRV (the standard deviation of 5-min mean R-R intervals) correlated with poor right and left ventricular performance and the predicted development of atrial fibrillation, mortality, and progression to valve surgery (3.1 relative risk).

Syncopy

Regarding neurally mediated syncope, there is evidence to suggest both withdrawal of sympathetic tone and increased vagal activity. The latter is manifested by bradycardia and increased high-frequency spectral HRV power (103). Despite the contribution of vagal activity to the bradycardia, chronic vagal tone and arterial baroreceptor sensitivity are not related to either the propensity to syncope (104) or the heart rate response during hypotension (104—106), although some authors have reported augmented heart rate response and variability in tilt-positive subjects (107—109).

Other conditions

Among diabetic subjects, a reduction in HRV during rest or during exposure to various reflex stimuli, even in the early stage of autonomic involvement, has been described (61, 110—112). Sleep apnea is another condition recently linked to abnormal HRV (113) with swings in HRV attributed to hypoxia. Controversial results have been published regarding HRV in hypertensive subjects, with the authors reporting normal (114—116) or low (117, 118) values. However, it has been found that, among hypertensives, a more stable heart rate resulting from an

ineffective baroreflex is associated with a more variable systolic blood pressure (119). Low HRV was found in treated hypertensive patients free of coronary artery disease (120). However, among hypertensive patients, a poor correlation between HRV and ventricular arrhythmias has been reported (114).

Intervention programs

Various intervention programs have been found to increase HRV. As was already mentioned, exercise training may increase cardiac vagal tone and hence HRV (56, 57, 121, 122). Biofeedback and relaxation tasks have also been found to be beneficial (123—126). Pharmacological intervention may affect the autonomic tone of the heart. The effects of beta-blockers were reviewed by Yusuf et al (127). Beta-adrenergic blockade seems to increase HRV, as reflected by augmented vagal activity (14, 128, 129). Vagomimetic drugs such as scopolamine have also been found to increase HRV (130, 131). Zuanetti et al (132) studied the effects of antiarrhythmic drugs on HRV. Amiodarone caused no changes, whereas flecainide and propafenone significantly reduced HRV. This effect may be related to the increased mortality reported for some of these agents (133) — further study is warranted.

Circadian variations in heart rate variability

HRV operates according to a circadian rhythm. The lowest HRV is observed in the morning (9), corresponding to the period of highest incidence of ventricular tachycardia and sudden death (31, 134, 135). A larger variability is found around awakening when heart rate changes rather abruptly from the nightly low to the much higher daily values. The actual transition usually starts earlier, but any anticipatory rise preceding awakening and the transition in the evening is smoother and slower. Lombardi et al (35) studied 24-h HRV spectrums in healthy subjects and in patients after a myocardial infarction. Healthy subjects were characterized by a predominant low-frequency component (sympathetic) during the day and high frequency (parasympathetic) at night. Patients after myocardial infarction had a significantly smaller high-frequency component during the night and a higher low-frequency component during the day. Symptomatic congestive heart failure was found to eliminate circadian variation in the various measures of HRV (136). Hypertension has also been found to reduce or eliminate HRV circadian variation (31, 136—139). Rizzini and his co-workers (139) found that long-term antihypertensive treatment with nifedipine or enalapril restored daytime-nighttime sympathovagal modulation in hypertensive pa-

tients. Although the results are consistent, further study is warranted to clarify the circadian variation in HRV in healthy and diseased cohorts.

Behavioral, physiological, occupational and environmental factors affecting heart rate variability

Over the last few years, an increasing number of laboratory studies have appeared on HRV (particularly, respiratory sinus arrhythmia) in the psychological and physiological literature. Each of these disciplines has utilized HRV as an index of vagal control of the heart, which is highly sensitive to both behavioral and physiological variables.

Wide variations in HRV at rest and during activity are commonly seen in healthy persons (21, 24). During rest instantaneous heart rate is regulated by the sympathovagal balance. With vigorous activity (140, 141) or stress, vagal tone is withdrawn and heart rate is regulated principally by adrenergic activity. Various activities during the day lead to a large variability in vagal tone and abrupt changes in HRV with smaller changes in heart rate (134). Thus activity needs to be controlled when HRV is analyzed. Besides physical activity, other factors that affect the autonomous nervous system are also capable of affecting HRV. Under laboratory conditions, mental load (142—145), including making complicated decisions (146), attention (147), and posture (148—150), have been shown to lower HRV. All these parameters should be properly controlled when HRV is analyzed. On the other hand, due to the potential effects of different kinds of stressors on HRV, the latter may be very useful as an objective indicator of acute strain (if resting or base-line HRV is also known).

In general, acute strain is assessed by heart rate or heart rate response to a given stressor. As has already been noted, HRV is predominantly influenced by cardiac vagal activity, while heart rate is also influenced by sympathetic activity (2). Furthermore, heart rate was found to be less variable than HRV between and within persons (134). Thus the study of the cardiovascular effects of exposure (acute or chronic) to a stressor may be misleading if only differences in heart rate are examined. In recent applications HRV measures have been employed in behavioral studies of stress, attention, learning, fatigue, and cognitive effort (151—156). Spectral analyses of HRV may be used to predict optimal worktime under a combination of enhanced mental load and other stressors.

The combined effects of sustained attention and heat exposure on HRV were assessed by Razmjou & Kjellberg (157). Heat exposure caused significant deteriora-

tion in simple reaction time and accuracy in a serial-choice reaction-time task. The effects of heat on response times and on HRV were correlated. HRV is affected by ambient temperatures. Parsons et al (158) analyzed the effects of environmental temperature (17 versus 27°C) on the resting HRV of healthy and diabetic subjects. HRV was greater in both groups at 27°C. Because cold wind on the face has been found to produce bradycardia via vagus nerve action (159), it is possible that cold wind exposure also results in increased HRV. In a study by Kunitake & Ishiko (160) a significant increase in power for the low (sympathetic) and high (parasympathetic) components of HRV accompanying bradycardia occurred by cooling the face to 0 and 10°C, whereas cooling the foot to 0°C yielded a significant increase in the sympathetic power component and a decrease in the parasympathetic component, without changing heart rate. In another study, by Lindqvist et al (148), thermal skin stimulation at 0.01—0.10 Hz (sympathetic frequency) increased both the sitting and standing power of the sympathetic component of HRV and decreased HRV. Exposure of patients with Raynaud's vibration syndrome and referents to cold demonstrated a cold-induced hyper-response of the parasympathetic nervous system and the alpha-2 adrenergic mechanism in the patients with Raynaud's vibration syndrome. This effect resulted from the activation of the sympathetic nervous system, which reduced HRV in the patients more than in the referents and resulted in their much lower HRV (161).

There are few studies of HRV in the workplace, and in general they have attempted to assess the effect of strain induced by various acute stresses on HRV. In Polish State Railway dispatchers it was found that the HRV coefficient fell during complicated and risky decisions (162). Professional bus drivers with higher absenteeism rates had higher levels of adrenaline and reduced HRV after 3.5 h of work compared with the HRV of those with lower absenteeism rates (163). In radio broadcasters, during direct broadcasting, HRV decreased (164). For parachute jumpers no difference in HRV between experienced and inexperienced jumpers was found during the jump (165). During flight the standard deviation of the heart rate tended to increase during medium interpretive actions and mental stress, and it decreased during high interpretive and emotional stress situations such as during takeoff and landing (166). Finally, for air traffic controllers a correlation was found between heart rate but not between HRV and the number of planes controlled (167). We could find only one study of chemical exposure and HRV. In a cross-sectional survey on 172 male workers exposed to lead, a significant dose-related decrease of HRV was observed (168). The authors concluded that an effect on the autonomic nervous system expressed as decreased HRV during deep breathing might be one of the earliest signs of lead toxicity.

Concluding remarks

Measuring HRV may provide valuable information for the occupational physician. HRV and its spectral components can be easily and noninvasively assessed. Despite the need for standardization in methodology to facilitate the interpretation and comparison of results, it is clear that there are individual differences in HRV which partly reflect differences in the degree of parasympathetic and sympathetic stimulation of the heart (or the heart responsiveness to stimulation). These differences are also reflected in the circadian variation of the spectral components of HRV. Measurements of HRV and the quantification of its spectral components are apparently a powerful predictor of cardiovascular morbidity and mortality. Therefore it may have a role in assessing the return to work of patients with ischemic heart disease. Studies in the workplace may also give an indication of the effects of various stresses of the work environment on such patients and, in fact, on asymptomatic workers. Various stresses leading to fatigue and decrements in performance have been associated with decreases in HRV. Therefore, analysis of the variation of R-R intervals may also be of value in defining the stresses present in various work stations and in identifying workers who are perhaps at increased risk for adverse consequences from such stress. Finally, a single study found that lead exposure was associated with a dose-related decrease in HRV. Further studies are warranted to support such findings and perhaps to extend them to other neurotoxic exposures found in the workplace.

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