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STATE-OF-THE-ART PAPER

Assessment of Autonomic Function in Cardiovascular Disease

Physiological Basis and Prognostic Implications

Marc K. Lahiri, MD, Prince J. Kannankeril, MD, Jeffrey J. Goldberger, MD, FACC

Chicago, Illinois

Certain abnormalities of autonomic function in the setting of structural cardiovascular disease have been associated with an adverse prognosis. Various markers of autonomic activity have received increased attention as methods for identifying patients at risk for sudden death. Both the sympathetic and the parasympathetic limbs can be characterized by tonic levels of activity, which are modulated by, and respond reflexively to, physiological changes. Heart rate provides an index of the net effects of autonomic tone on the sinus node, and carries prognostic significance. Heart rate variability, though related to heart rate, assesses modulation of autonomic control of heart rate and carries additional prognostic information, which in some cases is more powerful than heart rate alone. Heart rate recovery after exercise represents the changes in autonomic tone that occur immediately after cessation of exercise. This index has also been shown to have prognostic significance. Autonomic evaluation during exercise and recovery may be important prognostically, because these are high-risk periods for sudden death, and the autonomic changes that occur with exercise could modulate this high risk. These markers provide related, but not redundant information about different aspects of autonomic effects on the sinus node. (J Am Coll Cardiol 2008;51:1725–33) © 2008 by the American College of Cardiology Foundation

Numerous experimental and clinical studies have demonstrated that certain measures of autonomic function in the setting of structural cardiovascular disease are associated with an adverse prognosis. Specifically, both increased sympathetic and decreased parasympathetic activity have been associated with an increased risk for sudden death and/or susceptibility to ventricular arrhythmias. For example, there is an increased incidence of reperfusion-induced ventricular fibrillation with sympathetic stimulation in dogs (1). Conversely, parasympathetic stimulation decreases the incidence of ventricular fibrillation during ischemia in exercising dogs with myocardial infarctions (MIs) (2). In humans, beta-blockers decrease the incidence of sudden cardiac death after MI and in patients with congestive heart failure (3–9). This link between the autonomic nervous system and sudden death has stimulated interest in the evaluation of autonomic function as a potential method for identifying patients at high risk for sudden death.

Although autonomic modulation of the cardiovascular system is likely to be important in the pathogenesis of sudden cardiac death, it remains difficult to measure or quantify. Although a simple relationship between a physiological marker and autonomic "activity" would be attractive, the autonomic nervous system is extremely complex, making it difficult to elucidate such a simple relationship. A variety of markers have been proposed to reflect autonomic "activity," including heart rate, heart rate variability, heart rate recovery after exercise, baroreflex sensitivity, heart rate turbulence, plasma/coronary sinus catecholamine levels, muscle sympathetic nerve activity, and others. Because heart rate can be measured noninvasively and inexpensively, much focus has been placed upon analysis of heart rate and heart rate variability. It is therefore important to relate these markers to their physiological counterparts to understand how abnormalities in these measures may be implicated in the pathogenesis of sudden cardiac death. In a stable physiological state, the sympathetic and parasympathetic limbs can be considered to have tonic levels of activity which generally have antagonistic effects. Spontaneous physiological processes, such as respiration, further modulate the tonic level of activity. Finally, tonic activity responds reflexively to various "stresses," such as changes in blood pressure via the baroreflex mechanism and exercise. The study of these physiological responses of the sinus node depend upon intact sinus node function.

In the present paper, we review the following methods of autonomic assessment: heart rate (HR), heart rate variability (HRV) and heart rate recovery after exercise (HRR), with an emphasis on the physiological basis for each marker.

From the Division of Cardiology, Department of Medicine, Northwestern University, Chicago, Illinois.

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Abbreviations and Acronyms

HF = high frequency
HR = heart rate
HRR = heart rate recovery
HRV = heart rate variability
LF = low frequency
SDNN = standard deviation of normal R-R intervals
VLF = very low frequency

Their relationships to each other as well as their prognostic implications will be explored.

HR

The sinus node has an intrinsic rate of spontaneous depolarization, known as the intrinsic HR (10). The intrinsic HR is the HR measured in the absence of sympathetic and parasympathetic inputs (achieved by denervation or pharmacologic blockade). In healthy human subjects, this is approximately 100 beats/min and is age and gender dependent (10); endurance exercise-trained individuals may have a lower intrinsic HR (11). It is important to note that nonautonomic contributions to changes in HR exist: hypoxia, exercise, and temperature all can affect the intrinsic HR (12,13). Sympathetic and parasympathetic effects on the intrinsic HR predominantly determine the actual HR. Parasympathetic activation slows the HR via acetylcholine release from efferent vagal nerve discharge. In contrast, sympathetic activation accelerates the HR via circulating epinephrine, neural release of norepinephrine, or both (14). In a given stable physiological state, the sympathetic and parasympathetic inputs can be considered to have a tonic level of activity which determines the HR for that state. The influences of the sympathetic and parasympathetic nervous systems on HR have been proposed to be defined by the following formula: $HR = m \times n \times HR_0$, where m is the sympathetic influence (>1), n is the parasympathetic influence (<1), and HR_0 is the intrinsic HR (15). Thus, HR is determined by the intrinsic rate, and some measure of the tonic sympathetic and parasympathetic effects on the sinus node. Additionally, there are interactions between the sympathetic and parasympathetic limbs that determine their respective effects on HR. The effect of one limb is enhanced by increased activity of its counterpart, a phenomenon termed accentuated antagonism (16,17). In the absence of sympathetic activity, a given degree of parasympathetic stimulation will cause a given change in HR (from 100 to 90 beats/min, for example). The presence of sympathetic activity, though increasing HR (to 120 beats/min), allows the same degree of parasympathetic stimulation to cause a greater change in HR (from 120 to 105 beats/min).

Based on the model proposed by Rosenblueth and Simeone (15), HR seems to be a simple measure which can provide an index of the net effects of sympathetic and parasympathetic inputs to the sinus node. The HR consistently responds in an expected direction based on the underlying physiological state. That is, sympathetic stimulation consistently raises HR no matter what the stimulus is. Parasympathetic blockade raises HR, whereas parasympathetic stimulation lowers HR. In experimental settings, the R-R interval, reciprocally related to the HR, is directly related to vagal nerve activity (18). In a study of normal subjects exposed to a wide range of autonomic conditions, including upright tilt, exercise, epinephrine infusion, isoproterenol infusion, phenylephrine infusion, and parasympathetic blockade with atropine, HR responded in the expected direction for all subjects under all conditions tested (19). In the same study, none of the time and frequency domain measurements of HRV responded as consistently as the HR.

Although HR can be a powerful tool in the assessment of autonomic tone, it has obvious limitations. It provides a static index of the net effects of autonomic input to the sinus node, but no direct information regarding either sympathetic or parasympathetic input individually. For example, an HR of 110 beats/min demonstrates a net predominance of sympathetic effect on the sinus node. However, sympathetic stimulation, parasympathetic withdrawal, or various combinations of both may achieve this HR. Heart rate alone provides information regarding relative effects of autonomic tone in a given state, but not modulation or reflex activity.

The prognostic value of HR has been assessed in several large studies. High resting HR has been associated with increased all-cause mortality, death from cardiovascular disease, and particularly sudden cardiac death (20–23) in population-based studies. Jouven et al. (23) recently reported that a resting HR >75 beats/min in patients without clinical evidence of coronary disease conferred a nearly 4-fold risk for sudden cardiac death compared with those who had HR <60 beats/min over a 23-year follow-up period (23). Average HR on 24-h ambulatory electrocardiograms correlates with the incidence of new coronary events in patients with heart disease (24). In patients hospitalized with MI, high admission and discharge HRs are associated with an increase in both short- and long-term mortality (25–27). Comparison of trials of beta-blocker therapy after MI relates the reduction in resting HR to the percentage reduction in mortality in these trials (28). Thus, the simple measure of HR provides a global index of autonomic tone that has important prognostic significance. Despite the important role of HR and HR reduction in the prognosis of patients with cardiovascular disease, it is not widely recognized or used as a factor for risk assessment (29).

HRV

The oscillation in the intervals between consecutive heart beats has been described by several names, but heart rate variability has become the conventionally accepted term (30). Several methods of measuring the variation in HR have been developed, each of which falls under the broader description of being either "time domain" or "frequency domain" analyses. It should be noted that no one method has been identified as "superior" to the others, because no gold standard for HRV measurement exists; rather, these techniques may be considered to be complementary to each

other. Time domain measures of HRV are assessed with calculations based on statistical operations on R-R intervals (31). Commonly used measures include standard deviation of normal R-R intervals (SDNN), the root mean square of successive R-R interval differences (MSSD), and the percentage of normal R-R intervals that differ by >50 ms (pNN50). Although all these are measures of HRV, they are not interchangeable, nor do they necessarily reflect similar physiology. For example, the SDNN is related to the total power (variance) whereas both MSSD and pNN50 detect high frequency oscillations. However, it should be noted that all HRV is substantially suppressed by parasympathetic blockade.

Frequency domain measures use spectral analysis of a sequence of R-R intervals and provide information on how power (variance) is distributed as a function of frequency. Short-term recordings (2 to 5 min) yield up to 3 peaks in very low (0.003 to 0.04 Hz; VLF), low (0.04 to 0.15 Hz; LF), and high (0.15 to 0.4 Hz; HF) frequency ranges. Long-term (24-h) recordings allow measurement of a fourth, ultralow (<0.003 Hz; ULF) frequency range. It is important to note that HRV measurements made from long-term recordings during which circadian rhythms are present and patient activity is not controlled provide different physiological information than HRV measurements made from short-term recordings during which conditions are typically controlled or stable. The LF and HF powers are often reported in normalized (relative or fractional) units, which represent the relative value of each power in proportion to the total power (usually minus the VLF component). This is done to minimize the effect of changes in total power on the value of HF and LF components. As will be described subsequently, the HF component is thought to reflect the modulation of vagus nerve discharge caused by respiration, whereas the LF and VLF components represent the variation in R-R interval caused by more gradual interplay between sympathetic and parasympathetic activities. The physiological basis for the ULF component is not well defined (29).

Newer nonlinear analysis techniques have been applied to further characterize HRV. Although the aforementioned traditional HRV methods characterize variability in R-R intervals within certain time scales or frequencies, nonlinear analyses describe the structure of the variability independently of the scale studied. This concept relates to the observation that whereas different fluctuation patterns are observed within specific time periods or frequencies (using traditional techniques), other self-similar fluctuation patterns may also be elicited from a broad range of data scales. Such methods gather information not detected by traditional techniques. For example, although a short-term recording of a patient's normal R-R intervals will have an identical SD as the same set of R-R intervals that are randomly shuffled, the underlying structure of these two sets of R-R intervals are completely different (32). It is this underlying pattern that nonlinear analysis methods attempt to describe.

Although the interplay between the sympathetic and parasympathetic inputs is different for each of the HF, LF, and VLF components of HRV, it appears that parasympathetic effects play a very important role in all of them. Respiratory sinus arrhythmia is a reflection of parasympathetic effects on the sinus node (33), and the HF component of HRV coincides with the respiratory frequency. Parasympathetic blockade with atropine results in >90% decrease in the power contained in this frequency (33), whereas beta-adrenergic blockade with propranolol does not alter the HF power significantly (34). Atropine also reduces HRV in the LF (34–36), which could be ascribed to blockade of vagally mediated fluctuations in HR provoked by sympathetically mediated changes in arterial pressure (37). Furthermore, parasympathetic blockade has also been shown to reduce the VLF component of HRV by 92% (38). The mechanism behind the vagal influence on the VLF component is not clear; fluctuations in the renin-angiotensin-aldosterone system as well as variations in thermoregulatory mechanisms have been speculated.

One reason for the association of each limb of the autonomic nervous system with a different frequency range stems from the fact that the timing of the HR response to autonomic nerve activity is not identical for each limb. Although a burst of vagal nerve activity has a maximal effect at 0.6 s with a return to baseline within 1 s, a sympathetic burst has no effect for 1 s, a maximal effect at 4 s, and a return to baseline within 20 s (39). Both cardiac and peripheral sympathetic responses have a similar time delay (40). The short delay of the vagal cardiac responses allows the parasympathetic nervous system to modulate HR at all frequencies between 0 and 0.5 Hz, although the sympathetic system has significant gain only below 0.15 Hz (41). Muscle sympathetic nerve activity has been shown to fluctuate every 10 s (42), a period long enough for vascular smooth muscle and sinus node effectors to respond to released norepinephrine and modulate blood pressure and HR (43). This period corresponds to the LF range observed in HRV. The absolute and normalized LF powers have therefore been used as an index of sympathetic modulation of the heart rate, and the ratio of absolute LF to HF power has been used as an index of "sympathovagal balance" (40,44), although this term is poorly defined (19,37). Upright tilt, which increases sympathetic tone predominantly due to an increase in direct neural stimulation (33), consistently increases LF and LF/HF power and decreases time domain measures of HRV (45); beta-blockade blunts these changes (40).

Although the idea of a simple relationship between components of HRV and sympathetic or parasympathetic tone is attractive, several studies indicate that the relationship is more complex. Despite the fact that in certain settings there appears to be a direct relationship between certain measures of HRV and either sympathetic or para-

sympathetic activity, there are many examples where these relationships degenerate. For example, different modes of beta-adrenergic activation (exercise, catecholamine infusion, and upright tilt) result in divergent changes in frequency domain indices which have been reported to reflect sympathetic activity (34). Partial parasympathetic blockade and baroreflex-mediated sympathetic withdrawal to similar degrees (as determined by HR) result in diminished HF power, but to different degrees (46). A 10-fold difference in HF power demonstrated at different respiratory rates between 0.4 and 0.1 Hz (24 to 6 breaths/min) despite similar HR again shows that HF power can vary greatly despite similar levels of parasympathetic effect (47) and underscores the role of modulation of HR as the determinant of HRV. Baroreflex-mediated increased parasympathetic activity with phenylephrine may actually decrease HF power and time domain measures at high levels of stimulation (48) owing to saturation of the HRV response (49). The complex relationship between HRV and parasympathetic effect was demonstrated in normal subjects after beta-blockade (50). Using baroreflex-mediated increases and decreases in parasympathetic tone, it was shown that HRV initially increases with increasing parasympathetic effect until it reaches a plateau. Beyond this, further increases in parasympathetic effect actually decrease HRV. Of note, marked interindividual variability in this relationship was noted. Therefore, HRV should be considered to be a technique that characterizes the modulation of autonomic tone. Although there is some relationship between the modulation of autonomic tone and its tonic effect, this relationship may be quite complex and individualized. It has also been shown that genetic factors may be important determinants of HRV (51,52). It is therefore difficult to relate specific HRV measurements to either sympathetic or parasympathetic tone.

The relationship between HR and HRV has been well studied. In an animal study, vagal nerve stimulation decreased HR, with a clear correlation between stimulation intensity and change in R-R interval (53). Vagal stimulation also increased time and frequency domain measurements of HRV, but with little to no correlation between HRV measures and stimulus intensity. Sympathetic stimulation increased HR, with an inverse correlation between R-R interval and stimulus intensity, but there was no significant effect on time or frequency domain measures of HRV. Thus, in this animal model, HR and HRV responded differently to parasympathetic and sympathetic stimulation. Several studies in humans have examined this relationship as well. In one study of healthy subjects, a moderate correlation between mean HR and time domain measures of HRV on 24-h ambulatory electrocardiograms was demonstrated (54). However, several other investigations in patients with coronary artery disease or heart failure found no significant correlation between mean, minimum, or maximum HR and time or frequency domain measures of HRV (55–57).

The prognostic significance of HRV in cardiovascular disease is widely reported. Decreased HRV has been associated with increased mortality in patients after MI, with heart failure, and with ischemic and idiopathic cardiomyopathy (58–65). Large epidemiologic studies have also linked an increased risk of coronary heart disease, death, and cardiac mortality with decreased HRV in general populations (66–68). Although it is clear that low HRV has a negative prognostic impact, it is important to point out that causality and mechanisms have not been established. Animal studies have shown that interventions which improve the HRV profile do not necessarily decrease risk for sudden death. In a study of post-infarction dogs at high risk for ventricular fibrillation during exercise and ischemia, the dogs were treated with intravenous scopolamine, which at low doses has a parasympathomimetic effect. Although scopolamine increased the time and frequency domain measures of HRV, there was no decreased risk of ventricular fibrillation (69). In contrast, exercise training in a similar canine model increased HRV and conferred protection from sudden death (70). The pathophysiological link between reduced HRV and increased mortality is unclear. In the recent DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) (71), patients who had a recent MI, reduced ejection fraction, and impaired autonomic tone (as indicated by decreased HRV or high resting HR) did not have a survival benefit when treated with an implanted defibrillator, even though earlier studies have correlated early decreases in HRV within the first 48 h of MI with worse outcomes (72). On the other hand, cardiac resynchronization therapy with biventricular pacemakers has recently been shown to improve survival in a select group of patients with NYHA functional class III or IV heart failure and cardiac dyssynchrony (73). Although the exact mechanism of the benefit has not been identified, cardiac resynchronization therapy has been demonstrated to increase HRV (74); alterations in the autonomic modulation of the heart could play a role in the improved survival. This connection was further strengthened by a recent study of 113 patients with NYHA functional class III or IV heart failure, which found that those with improved time domain measures of HRV (by the SDNN method) 4 weeks after initiation of cardiac resynchronization therapy had better outcomes compared with those with less pronounced responses (75). Thus, HRV appears to be an important marker of mortality risk for sudden cardiac death, and some (but not all) interventions that improve HRV may also reduce the risk of sudden cardiac death. A causal relationship between low HRV and death has not been established.

Comparisons between the prognostic significance of HR versus HRV have been assessed in a few large studies. In a study of 808 patients after MI, HRV was an independent and better predictor of mortality compared with mean HR (58). A subsequent study, performed in the thrombolytic era, found that mean HR on 24-h recordings was nearly as good a predictor of all-cause mortality, as well as cardiac and

sudden death, as HRV (76). In a study of 6,693 patients with 24-h Holter recordings, the adjusted relative risk for sudden death over a 2-year period was similar for low HRV and high minimum HR, but mean HR had no relation to sudden death (77).

Heart rate variability is a complex measure of modulation of HR that incorporates sympathetic effects, parasympathetic effects, and their interaction. Heart rate variability appears to be related to HR under certain conditions. It is an important marker of adverse prognosis in patients with cardiac disease and in normal populations. It is important to delineate the supplemental prognostic information contained in HRV over HR. Further understanding of the pathophysiological relationship of low HRV to mortality will be useful in developing strategies that could increase HRV and may improve survival.

HR Recovery

Exercise is associated with increased sympathetic and decreased parasympathetic activity (78–80). The period of recovery after exercise is accompanied by further dynamic changes in autonomic tone which are clinically characterized by the gradual return of HR to its previous resting level. This period of HRR results from a combination of sympathetic withdrawal and parasympathetic reactivation. Earlier studies have provided conflicting data as to which of these 2 processes plays the greater role in the physiology of early HRR. Savin et al. (81) studied the HRR of 6 men in whom selective autonomic blockade was administered on different days before the initiation of exercise. They interpreted their findings as suggesting that "sympathetic withdrawal contributes more to HRR soon after peak exercise cessation, with parasympathetic activation playing a greater role later in recovery at lower rates." In contrast, Imai et al. (82) reported that "the initial HRR within 30 seconds is mediated primarily by vagal reactivation." In that study, the investigators evaluated groups of young (age 20 years), trained athletes, older (age 55 years) subjects with congestive heart failure, and age-matched sedentary controls. Atropine was administered before exercise, and subjects exercised submaximally to anaerobic threshold. Heart rate recovery was evaluated only up to 2 min. More recent data also have demonstrated that parasympathetic activation plays a substantial role early in HRR after high-intensity exercise in normal subjects. Kannankeril et al. (83) analyzed HR in 10 healthy individuals during peak exercise and recovery under normal physiological conditions as well as during selective parasympathetic blockade with atropine. These data demonstrated that even during peak high-intensity exercise, the parasympathetic system has a small but significant effect on HR, indicating that parasympathetic withdrawal is not complete under such conditions. Upon cessation of exercise, augmentation of parasympathetic effects on HR occurred rapidly within the first minute. The intensity of parasympathetic reactivation steadily increased further until 4 min into recovery, after which time parasympathetic effects on HR remained relatively constant. The question of how much sympathetic withdrawal contributes to HRR after exercise was addressed in a recent study by Sundaram et al. (84). In that study, HRR after submaximal exercise was analyzed in 28 healthy subjects during normal physiological condition, as well as during selective beta-adrenergic blockade with propranolol, selective parasympathetic blockade with atropine, or double blockade with both agents. In the first minute of recovery, there was no difference in HRR between the conditions of parasympathetic blockade and double blockade, suggesting that beta-adrenergic withdrawal is not a significant factor in HRR within the first minute. Interestingly, there was a significant component of HRR seen in the group undergoing double blockade. This implies that there is a non–beta-adrenergic, nonparasympathetic component of HRR. Possible mechanisms could include changes in alpha-adrenergic tone, atrial stretch, or temperature changes. Collectively, these data suggest that early HRR after exercise is complex but predominantly due to parasympathetic reactivation, with sympathetic and nonautonomic components probably playing lesser roles.

There are compelling data to support the prognostic significance of HRR following exercise. Recently, Jouven et al. (23) reported that an HRR <25 beats/min after the first minute of recovery conferred a relative risk of 2.2 for sudden cardiac death compared with the highest-percentile HRR group (>40 beats/min) (23). In an earlier study, Cole et al. (85) defined an abnormal HRR as a decrease in HR from peak exercise to 1 min into recovery of 12 beats/min or less. In a cohort of 2,428 subjects without a prior history of heart failure, coronary revascularization, coronary angiography, or exercise testing, there was a 4-fold risk of death in those with abnormal HRR. After adjustment for age, gender, medications, perfusion defects on thallium scintigraphy, standard cardiac risk factors, resting HR, change in HR with exercise, and workload achieved, there was still a 2-fold risk of death in those with abnormal HRR. Though that study specifically investigated HRR after peak symptom-limited exercise, there are also data to suggest that impaired HRR after submaximal exercise has prognostic value as well. Cole et al. (86) defined abnormal HRR after submaximal exercise as a change of ≤ 42 beats/min from peak HR to that measured 2 min into recovery. In that study, patients with abnormal HRR after submaximal exercise incurred a relative risk of death of 2.58 during 12 years of follow-up. This increased risk remained significant after adjustment for standard risk factors, fitness, and resting and exercise HR. These data imply that HRR has prognostic implications under a broad range of exercise conditions. Furthermore, this prognostic value has been shown to represent risk independent of that based on the Duke Treadmill Score, suggesting that additive benefit may be derived from incorporating such measurements into standard treadmill test reporting (87). Interestingly, there is

evidence that impaired HRR after exercise may be a modifiable risk factor. This was demonstrated in a recent study (88) that retrospectively studied HRR in 55 patients participating in phase II cardiac rehabilitation, an activity that has been shown to improve survival in patients following MI (89,90). The HRR was analyzed in 55 patients who had symptom-limited treadmill tests both before and after completing phase II cardiac rehabilitation. After completing cardiac rehabilitation, these patients had significantly lower resting HR compared with pre-rehabilitation measurements (65 beats/min vs. 69 beats/min; $p = 0.01$) and had a 26% improvement in their HRR during the first minute after exercise (15.4 beats/min pre-rehabilitation vs. 19.4 beats/min post-rehabilitation; $p < 0.001$). Such findings would suggest that cardiac rehabilitation improves parasympathetic function, which may at least in part contribute to the decreased mortality seen among these patients.

Why abnormal HRR after exercise is associated with an increased risk of death is not completely understood. One contributing factor could be that impaired HRR appears to correlate with the presence of underlying ischemic coronary artery disease. Georgoulias et al. (91) found that patients with impaired HRR (as defined by an HR decrease <21 beats/min 1 min after abrupt cessation of exercise) had a higher myocardial perfusion score (indicating more ischemia) on nuclear stress testing compared with patients with normal HRR. Therefore, patients with impaired HRR may be more likely to have underlying active ischemia, which could at least in part account for their higher mortality risk. However, ischemia does not appear to be the only factor contributing to their risk. In a prospective study of 2,935 patients who had both exercise testing and coronary angiography, Vivekananthan et al. (92) found that impaired HRR was predictive of mortality independent of the severity of coronary artery disease seen on angiography. Given the substantial role that parasympathetic activation plays in early recovery and the prognostic significance of diminished parasympathetic tone at rest, it is tempting to infer that parasympathetic "insufficiency" is implicated in the increased mortality risk in patients with abnormal HRR. However, there are no data that directly implicate diminished parasympathetic tone as the underlying mechanism behind the increased risk of death in such patients.

Heart rate recovery after exercise is emerging as a new and important prognostic index. Further investigation into the physiological basis and prognostic significance of autonomic function during recovery is warranted to better delineate its relation to the risk for total mortality and sudden cardiac death.

Physiological Construct

Given the wealth of information available regarding the physiological and prognostic significance of HR, HRV, and HRR, it is important to synthesize this information into a useful framework that can form the foundation for further study. The following simplified model may be useful to conceptualize autonomic control of HR and is shown schematically in Figure 1. Although it is likely that autonomic control of the HR also reflects autonomic effects on cardiac parameters other than the sinus node, it is important to recognize that there is differential innervation within the heart and that there may be differing effects in different regions of the heart (93).

In its simplest formulation, HR is used to represent sympathovagal balance. Although this term is poorly defined, it is reasonable to use it as a measure of the net effects of the sympathetic and parasympathetic inputs into the sinus node. This concept is captured by HR. The HRV is then used to quantify the modulation of the sympathetic and parasympathetic inputs. The HRR represents the responsiveness and/or activity of the parasympathetic nervous

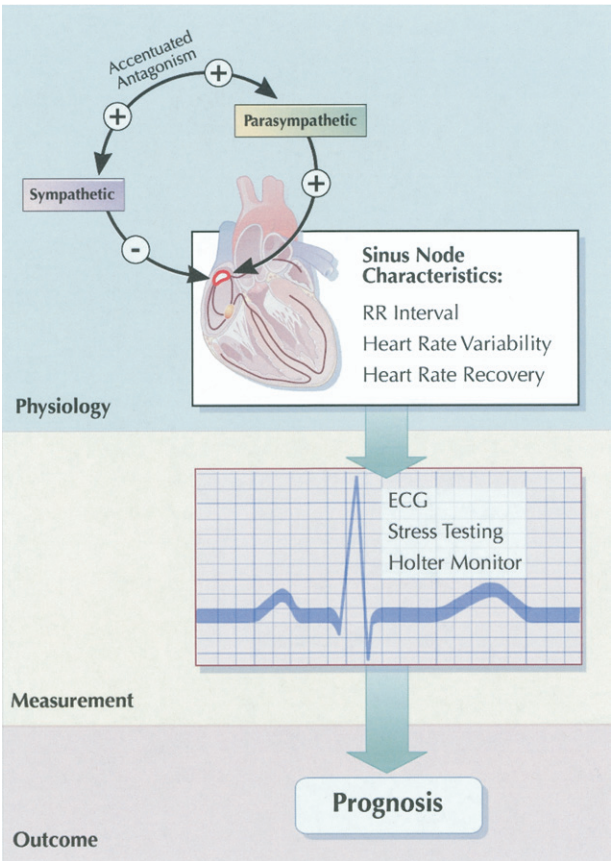

Figure 1 **Schematic Diagram Showing Physiological Parasympathetic and Sympathetic Effects**

This diagram shows the physiological parasympathetic and sympathetic effects on the sinus node to increase or decrease, respectively, the R-R interval and their interaction ("accentuated antagonism"). These inputs and their changes with physiological activities (i.e., respiration, exercise) influence the R-R interval, heart rate variability, and heart rate recovery. These characteristics can be quantified through short-term electrocardiogram (ECG) recordings, Holter monitoring, or stress testing. The heart rate, heart rate variability, and heart rate recovery that are measured through these tests provide prognostic information in patients with cardiovascular disease. Figure illustration by Rob Flewell.

system to cessation of exercise. Other parameters of the responsiveness of the autonomic system, such as baroreflex sensitivity and heart rate turbulence have also been shown to provide prognostic information. It should be noted that all of these techniques rely upon normal sinus node function and adequate recording of sinus node activity. The presence of sinus node dysfunction and significant atrial and/or ventricular ectopy in elderly patients with heart disease could make these measurements less useful.

Although it is likely that these indices and the related physiologies are dependent upon each other, they also each have distinct and independent physiological significance.

Issues for Further Study

Although there are compelling data that parasympathetic activity is associated with improved survival, the precise mechanism of parasympathetic protection is not clear. An attractive hypothesis is that parasympathetically induced changes in cardiac electrophysiology exert antiarrhythmic effects. It is well known that parasympathetic stimulation affects sinus nodal automaticity and AV nodal dromotropy (94,95). Several studies have also demonstrated changes in ventricular refractoriness with parasympathetic stimulation or blockade (96,97); parasympathetic effects on ventricular refractoriness may be antiarrhythmic. However, it is possible that some of the benefits of parasympathetic tone are mediated by other mechanisms, such as reduction in HR. Vanoli et al. (2) studied the effects of vagal stimulation and vagal stimulation plus atrial pacing on the prevention of exercise and ischemia-induced ventricular fibrillation in dogs with a healed MI. Although vagal stimulation prevented most episodes of ventricular fibrillation, when atrial pacing was instituted to prevent the HR reduction associated with vagal stimulation, approximately one-half of the animals had ventricular fibrillation. This suggests that the benefits of vagal stimulation may be partially due to an HR-lowering effect and partially due to other parasympathetic effects. It seems likely that most of these other protective effects of parasympathetic tone on sudden death would result from electrophysiological effects occurring in the ventricle. Yet, HR, HRV, and HRR all measure autonomic effects on the sinus node and may not provide adequate assessment of parasympathetic effects in the ventricle. Differential autonomic effects have been noted in various regions of the heart (93). Divergent changes in Q-T and R-R intervals (reflecting differential effects on ventricular repolarization and heart rate) beyond that simply explained by rate dependence can be observed in healthy subjects (98). Cervical vagal stimulation does not change HRV and BRS after vagal denervation of the atria in dogs, whereas changes in ventricular refractoriness are still induced (44). These studies highlight the fact that autonomic effects on the sinus node are not necessarily predictive of their effects on the ventricles.

The role of exercise and the associated changes in autonomic function in the pathophysiology of sudden death require further exploration. The risk of cardiac arrest and sudden death is substantially increased during and immediately after vigorous activity (99,100). Experimental data have shown that animals susceptible to ventricular fibrillation have greater reductions in HRV (parasympathetic modulation) during exercise compared with nonsusceptible animals (101). Interestingly, there was no significant difference between the 2 groups at rest. The HRR may provide further information regarding the risk for arrhythmias that occur in the setting of exercise or recovery.

Reprint requests and correspondence: Dr. Jeffrey J. Goldberger, Northwestern Memorial Hospital, 251 East Huron Street, Chicago, Illinois 60611-2950. E-mail: j-goldberger@northwestern.edu.

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