Autonomic Nervous System Interaction With the Cardiovascular System During Exercise

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There is considerable recent evidence that parameters thought to reflect the complex interaction between the autonomic nervous system and the cardiovascular system during exercise testing can provide significant prognostic information. Specific variables of great importance include heart rate (HR) response to exercise (reserve), HR recovery after exercise, and multiple components of HR variability both at rest and with exercise. Poor HR response to exercise has been strongly associated with sudden cardiac death and HR recovery from a standard exercise test has been shown to be predictive of mortality. In addition, there are limited studies evaluating the components of HR variability at rest and during exercise and their prognostic significance. Research continues seeking to refine these exercise measurements and further define their prognostic value. Future findings should augment the power of the exercise test in risk-stratifying cardiovascular patients.

The purpose of this review is to provide an overview of the use of clinical exercise testing to evaluate autonomic nervous system (ANS) interaction with the cardiovascular system (CVS) (Fig 1). This topic has garnered much interest over the last decade because there is mounting evidence that parameters thought to reflect the complex interplay between the ANS and the CVS during exercise testing can provide significant prognostic information. We will present a basic physiological understanding of the ANS, as well as the measurements that have been used to assess ANS interaction with the CVS. Specifically, we will discuss heart rate (HR) response to exercise (reserve), HR recovery (HRR) after exercise, and multiple components of HR variability (HRV) both at rest and with exercise. We will then review the strong evidence that has emerged over the last decade, linking poor HR response to exercise with sudden cardiac death, as well as the evidence demonstrating the significant prognostic value of HRR from a standard exercise test. In addition, we will discuss the limited studies evaluating the components of HRV at rest and during exercise and their prognostic significance.

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Methods

We performed a systematic review using PubMed (keywords: exercise test, ANS, HRR, HRV, and prognosis) and scans of citations in relevant papers that were gathered manually. The main results from this process are the 26 studies summarized in Table 1 using critical features that help to qualify their results and to find common points for consensus.

Background

The ANS is predominantly an efferent system transmitting impulses from the central nervous system (CNS) to peripheral organs. Its effects include control of HR and force of heart contraction, constriction and dilatation of blood vessels, contraction and relaxation of smooth

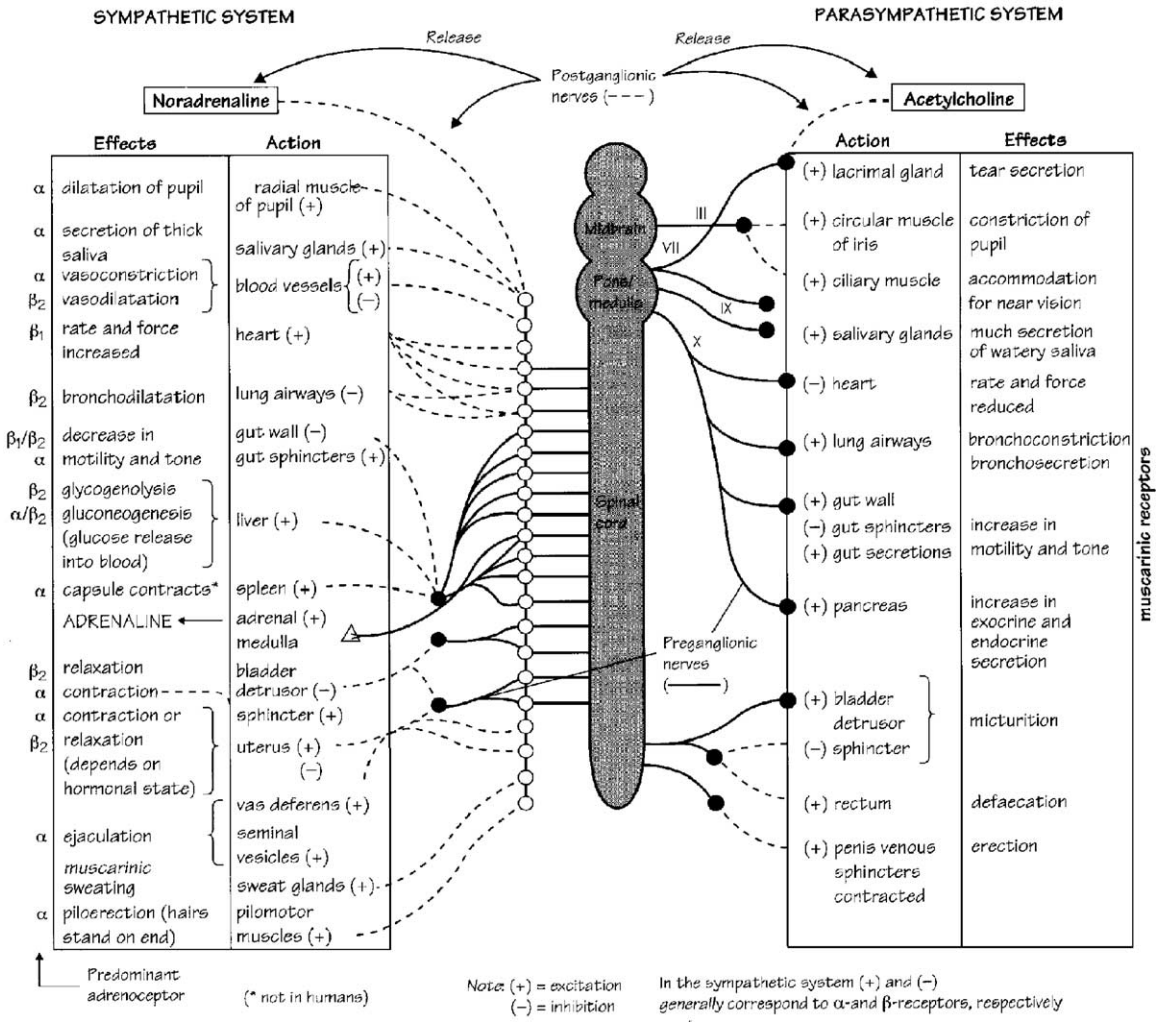

Fig 1. Autonomic Nervous System. Reprinted with permission from Neal MJ, Medical Pharmacology at a Glance, Blackwell Science [68].

muscle in various organs, and glandular secretions. Autonomic nerves constitute all of the efferent fibers that leave the CNS, except for those that innervate skeletal muscle. There are some afferent autonomic fibers (ie, from the periphery to the CNS) that innervate the baroreceptors and chemoreceptors in the carotid sinus and aortic arch, which are important in the control of HR, blood pressure, and respiratory activity. The ANS is divided into 2 separate divisions, parasympathetic and sympathetic, based on anatomical and functional differences (Table 1).

Parasympathetic Nervous System

The preganglionic outflow of the parasympathetic nervous system (PNS) arises from the brain stem and is known as the craniosacral outflow. The vagus nerve (or Xth cranial nerve) carries fibers to the heart and lungs (as well as other organs) and is the primary parasympathetic innervation of these organs. The PNS is largely concerned with conservation and restoration of energy by causing a reduction in HR and blood pressure and by facilitating digestion and absorption of nutrients and discharge of wastes. The chemical transmitter at synapses in the PNS

Table 1. Summary of Studies Discussed in the Review

Reference	Year	Sample size	Study design	Age	Patient population	Methods	Conclusions
HR response to exercise							
[26]	2005	5713	Cohort	42-53 y	Asymptomatic working men with no history of CVD	Three successive bicycle workloads: 2 min at 82 W, 6 min at 164 W, and the last 2 min at 191 W, for a maximum 10-min test with 10-min recovery	Resting HR >75 beats per minute, increase during exercise <89 beats per minute, and decrease <25 beats per minute after exercise were significant predictors of sudden cardiac death
[23]	1998	231	Cohort	Mean 57 y	Patients not taking β-blockers referred for symptom-limited exercise echo; 63% men	Bruce or modified Bruce protocol treadmill testing	Chronotropic incompetence was predictive of death, nonfatal MI, unstable angina, and late (>3 mo after exercise test) myocardial revascularization
[24]	1996	1575	Cohort	Mean 43 y	Framingham cohort; men free of coronary heart disease who were not taking β-blockers	Bruce protocol submaximal treadmill testing	Attenuated HR response to exercise is predictive of increased mortality and CHD incidence
[12]	1987	6238	Cohort	34-60 y	Asymptomatic hypercholesterolemic white men	Progressive submaximal treadmill testing	Smaller increases in HR were observed during treadmill test in physically active men and smokers; HR of smokers remained elevated after exercise, HR of active men rapidly returned to baseline; resting HR and BP levels were significant predictors of HR response
[15]	1984	23000	Systematic review/ meta-analysis	5-81 y	Healthy volunteers	Variable	Age accounted for 75% of the variability in maximal HR; other factors tested added only 5% and included mode of exercise, level of fitness, and continent of origin but not sex; trained individuals had significantly lower maximal HR than untrained subjects.
[20]	1982	12	Descriptive/ cohort	Mean 50 $\pm$ 4 y	Men w/ no history of major illness or taking medications studied after 10-d recumbency	Supine and upright graded maximal exercise testing before and after bedrest	Peak HR increased significantly after bedrest; orthostatic stress limits exercise tolerance after bedrest
[22]	1975	2700	Cohort	Mean 40-50 y (~48)	Subjects referred for routine screening treadmill test as part of annual physical examination; 82% men	Maximum treadmill testing	Chronotropic incompetence and ST-segment depression during treadmill test were significant predictors of future coronary events

HR response to exercise							
[21]	1974	5	Descriptive/ cohort	Mean 21 y	5 healthy Peruvian male medical students who had lived lifelong at sea level	Upright bicycle ergometer testing; submaximal work for 8 min and maximal work sustained to exhaustion, usually 4-5 min	Reduction of maximal HR occurred at 4600 m, compared with sea level which was partially reversed by atropine
HR recovery							
[37]	2000	9454	Cohort	Mean 53 ± 11 y	Asymptomatic patients older than 29 y w/o history of CHF or valvular disease and pacemaker implantation; 78% male	"Symptom-limited" treadmill testing using primarily Bruce or modified Bruce protocols	Failure of HR to decrease by more than 12 beats per minute during the first min after peak exercise and treadmill exercise score; both were independent predictors of mortality
[36]	2000	5234	Cohort	Mean 43 ± 10 y for normal HRR, Mean 47 ± 11 for abnormal HRR	Adults w/o evidence of CVD (Lipid Research Clinics Prevalence Study)	Bruce or modified Bruce protocol treadmill testing	After submaximal exercise, abnormal HR recovery (<43 beats per minute at 2 min) predicts death even after adjusting for standard risk factors, fitness, and resting and exercise HR
[30]	2000	9	Descriptive/ cohort	24-46 y	Healthy volunteers; 56% male	Bruce protocol treadmill testing; exercise was repeated a minimum 24 h later, but stopped 2 stages of the Bruce protocol less than that achieved during maximal exercise	First-order decay is an inadequate model for HR recovery after max exercise but may be reasonable for sub-max levels.
[35]	1999	2428	Cohort	Mean 57 ± 12 y	Adults w/o CHF, coronary revascularization, or pacemakers; 63% men	Bruce and modified Bruce treadmill testing	Delayed decrease in HR during first min after graded exercise is a significant predictor of mortality, independent of workload, presence/ absence of myocardial perfusion defects, and changes in HR during exercise
[32]	1999	74	Case control	Mean 51 ± 5 in controls; 57 ± 8 in CHF class C cases	18 healthy subjects, 18 patients w/ coronary artery disease, 38 patients w/ CHF	Electromagnetically braked cycle ergometer testing in the upright position using a ramp protocol; the ramp rates used were 20 W/min in the control group, 20 or 15 W/min in the group of patients with CAD, and 10 W/min in the group of patients w/ CHF	Presence and degree of heart disease has no effect on ventilation or HR recovery time

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Table 1 (*continued*)

Reference	Year	Sample size	Study design	Age	Patient population	Methods	Conclusions
[28]	1994	37	Cohort	NA	Eight normal volunteers, 20 patients w/ CHF, and 9 cross-country skiers	Maximal exercise testing with recovery	Vagally mediated HR recovery after exercise is accelerated in well trained athletes but blunted in patients w/ CHF
[31]	1989	6	Descriptive/ cohort	NA	Sedentary young men	Cycle ergometer testing at 3 periods: 21% ± 2.8%, 43% ± 2.1%, and 65% ± 2.3% of V_{O_2} max, respectively (mean ± SE)	HR and norepinephrine levels increase with cycle ergometer exercise; HR recovery after exercise is initially due to vagal input and then due to decreased sympathetic tone (lower norepinephrine)
[29]	1982	6	Descriptive/ cohort	Mean 31 y	Healthy male students and laboratory staff	Treadmill testing in 3-min stages: 3 MPH w/ 5% grade, 4 MPH w/ 10% grade, and 7 MPH w/ 10% and 15% grade; exercise was symptom-limited and recovery was 10 min	HR recovery after peak exercise occurred in an exponential manner irrespective of treatment with atropine, propranolol, or both
HR variability							
[61]	2004	1772	Cohort	Mean ~59 y	Post-MI patients (EMIAT and ATRAMI trials); 86% men	Continuous Holter ECG recordings for 24 h during normal daily activities	Low frequency HRV is a significant independent predictor of mortality
[69]	2004	121	Cohort	64 ± 9	Women patients who survived hospitalization for acute MI and/or underwent a percutaneous transluminal coronary angioplasty or a CABG	Continuous Holter ECG recordings for 24 h during normal daily activities	Low HRV is a predictor of long-term mortality among middle-aged women with coronary heart disease when measured 36 months after hospitalization for an acute coronary syndrome, even after controlling for established clinical prognostic markers
La Rovere MT, *Circulation,* Istituto Scientifico di Montescano, Pavia, Italy	2003	202	Cohort	52 ± 9 y	Subjects w/ moderate to severe CHF: LVEF 24 ± 7%, NYHA class 2.3 ± 0.7	Resting ECG and lung volume (inductance plethysmography) recordings obtained, during 8 min of spontaneous respiration and during 8 min of controlled breathing at 12 to 15 breaths per min; selection made of 5-min section free of artifacts or marked sudden changes in respiration or R-R interval for each condition	Reduced short-term LF HRV power during controlled breathing is a powerful predictor of sudden death in patients with CHF

HR variability							
[65]	1996	10	Descriptive/ cohort	Mean 44 y	Healthy subjects; 50% men	Bicycle ergometer symptom limited testing w/ continuous load increase of 10 W/min; on second occasion >24 h later samplings made at 40% and 70% of max workload w/ subject working for 6 min at each level before sampling to achieve steady state	HRV of sinus rhythm in healthy individuals has characteristics suggestive of low-dimensional chaos-like determinism, which is modulated but not eliminated by inhibition of autonomic tone or by exercise; the dominant Lyapunov exponent characterizes HRV independent of other investigated measures
[64]	1992	24	Case control	NA	14 male sedentary controls, 10 male long-distance runners	Continuous ECG recordings were obtained during the following physiological maneuvers: 45-min supine rest; 10-min standing; 15-min steady-state exercise at 50% max workload, and 15 min while supine in postexercise recovery	Resting HF HRV power higher in athletes; resting LF HRV lower in athletes; no group differences observed during upright posture or exercise, but LF/HF area ratio returned to pre-exercise levels within 5 min of recovery in athletes
[59]	1989	32	Descriptive/ cohort	NA	Normotensive male post-MI patients	Continuous Holter ECG recordings at rest and after phenylephrine injection	The 3 Holter variables PNN50, RMSSD, and HF HRV power showed strong correlation with each other; baroreflex sensitivity showed weak correlation w/ these variables
[31]	1989						
[70]	1987	808	Cohort	<70 y	Post-MI patients who survived CCU care	Continuous 24-h ECG during normal daily activities recorded 11 $\pm$ 3 d after acute MI	In post-MI patients, relative risk of mortality was 5.3 times higher in group with HRV <50 milliseconds, compared with HRV >100 milliseconds; HRV remained a significant predictor of mortality after adjusting for clinical, demographic, other Holter features and ejection fraction
Baroreflex sensitivity							
[3]	2001	1071	Cohort	<80 y	Recent (<1 mo history of MI in sinus rhythm, w/ no contraindications to exercise, no unstable angina, no ischemia requiring CABG, and no CHF	Continuous 24-hour ECG recordings; BRS assessed using the phenylephrine method	Non sustained ventricular tachycardia, depressed BRS, and HRV were all significantly and independently associated with increased mortality. The combination of all 3 risk factors increased risk of death by 22 times
[59]	1989						

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Table 1 (*continued*)

Reference	Year	Sample size	Study design	Age	Patient population	Methods	Conclusions
ANS and Sudden Cardiac Death							
[26]	2005						
[39]	2002	2967	Cohort	Mean 43 y	Framingham Offspring Study participants free of CVD; 47% men	Submaximal treadmill testing using Bruce protocol; exercise terminated when subjects achieved target HR, defined as 85% of the age- and sex-predicted max HR; after peak exercise, patients immediately got off the treadmill and rested in a supine position for 4 min of recovery	Continuous HR recovery indices not associated with CHD and CVD events; top quintile of HR recovery at 1 min after exercise associated w/ decreased CHD and CVD
[27]	1998	1284	Cohort	<80 y	Recent (<1 mo) history of MI in sinus rhythm, w/ no contraindications to exercise, unstable angina, ischemia requiring CABG, CHF, cardiomyopathy, IDDM, and valve disease	Continuous 24-h ECG recordings; BRS assessed using the phenylephrine method	Low values of either HRV (SDNN <70 milliseconds) or BRS (<3 · 0 milliseconds per mm Hg) carried a significant multivariate risk of cardiac mortality

Abbreviations: *BP*, blood pressure; *CAD*, coronary artery disease; *BRS*, baroreflex sensitivity; *CABG*, coronary artery bypass graft; *IDDM*, insulin-dependent diabetes mellitus.

is acetylcholine (Ach); thus, nerve fibers that release Ach from their endings are described as cholinergic. The specific Ach receptors have been further subdivided pharmacologically by the actions of the alkaloids muscarine and nicotine on these receptors. Postganglionic parasympathetic nerve endings, the response of which to Ach is mimicked by muscarine, are referred to as muscarinic Ach receptors, and postganglionic receptors, the response of which to Ach is mimicked by nicotine, are termed *nicotinic Ach receptors*. Vagal tone declines with aging, and the only physiological stimulus that has been found to increase vagal tone is regular dynamic exercise.

Sympathetic Nervous System

The cell bodies of the sympathetic preganglionic fibers are in the lateral horns of spinal segments T1 through L2, which comprise the thoracolumbar outflow of the sympathetic ganglionic chains. The adrenal medulla is innervated by preganglionic fibers, and therefore, adrenaline is released from the gland by stimulation of nicotinic Ach receptors. At most postganglionic sympathetic endings, the chemical transmitter is noradrenaline, which is present in the presynaptic terminal as well as in the adrenal medulla. The synthesis and storage of the catecholamines adrenaline and noradrenaline (which are synthesized from the essential amino acid phenylalanine) in the adrenal medulla is similar to that of sympathetic postganglionic nerve endings, but most noradrenaline in the adrenal medulla is converted to adrenaline. The adrenal medulla responds to nervous impulses in the sympathetic cholinergic preganglionic fibers by hormonal secretion. In situations involving physical or psychological stress, much larger quantities are released.

In contrast to the parasympathetic system, the sympathetic system enables the body to respond to challenges to survival (fight or flight) or situations of hemodynamic collapse or respiratory failure. Sympathetic responses include an increase in HR, blood pressure, and cardiac output; a diversion of blood flow from the skin and splanchnic vessels to those supplying skeletal muscle; bronchiolar dilation; and a decline in metabolic activity. The actions of catecholamines are mediated by α and β receptors. β_1-Adrenoceptor–mediated effects in the heart, which include increased force and rate of contraction, are differentiated from those producing smooth muscle relaxation in the bronchi and blood vessels, which are β_2-mediated effects. Table 2 summarizes the various cardiovascular (CV) and pulmonary responses to parasympathetic and sympathetic stimulation.

Autonomic Nervous System Balance in Exercise Treadmill Testing

Much can be demonstrated about ANS balance by evaluating several discrete aspects of the cardiopulmonary exercise treadmill test, including the following:

1. Pretest rest period
2. The HR response to dynamic exercise
3. Heart rate recovery from the exercise test
4. Heart rate variability
    a. The high-frequency (HF) component of HRV
    b. The low-frequency (LF) components of HRV

Table 2. Responses of the Cardiovascular/Pulmonary Organs to Autonomic Stimulation

Organ	Sympathetic stimulation	Parasympathetic stimulation
Heart	Increased HR β_1 (and β_2)	Decreased HR
	Increased force of contraction β_1 (and β_2)	Decreased force of contraction
	Increased conduction velocity	Decreased conduction velocity
Arteries	Constriction (α_1)	Dilation
	Dilation (β_2)	
Veins	Constriction (α_1)	
	Dilation (β_2)	
Lungs	Bronchial muscle relaxation (β_2)	Bronchial muscle contraction
		Increased bronchial gland secretions

Rest

The average resting HR in adulthood is approximately 72 beats per minute, with a reference range of 50 to 90.[1,2] A resting sinus HR of 90 beats per minute or greater represents sinus tachycardia, and a resting sinus HR of 50 beats per minute or lower represents sinus bradycardia. Parasympathetic input from vagal tone seems to contribute largely to the maintenance of resting HR. Vagal influence is clearly demonstrated in heart transplantation, after which, the donor heart is extrinsically denervated. Thus, the heart is not responsive to the normal actions of the parasympathetic and sympathetic systems. The absence of vagal tone results in high resting HRs in these patients (100-110 beats per minute) and the relatively slow adaptation of the heart to a given amount of submaximal work. In normal subjects, the major physiological means of enhancing vagal tone and lowering resting HR is regular dynamic exercise. Lower resting HR (ie, higher vagal tone) has been shown in many studies to be associated with lower mortality. Impairment of vagal tone and elevated resting HR occurs with aging, deconditioning, altitude, and avoidance of gravitational stress such as what occurs with bed rest.

Parasympathetic function has also been measured using baroreflex sensitivity. The slope of a regression line between the change in blood pressure and the change in R-R interval on the electrocardiogram (ECG) after administration of a vasoactive agent such as phenylephrine quantifies the vagally mediated baroreceptor reflex control of HR.[3] Baroreflex sensitivity measures the ability of the parasympathetic system to respond reflexively to a discrete stimulus and is a static measurement.

A hyperadrenergic state with increased sympathetic tone and decreased parasympathetic tone while at rest can occur as a primary or secondary condition. Examples of a primary hyperadrenergic state include inappropriate sinus tachycardia and postural orthostatic tachycardia syndrome. Inappropriate sinus tachycardia, which is defined as a persistent increase in HR greater than 100 beats per minute outside of appropriate psychological, pharmacological, or pathological stressors, is thought to be a result of enhanced automaticity of the sinus node.[4,5] Postural orthostatic tachycardia syndrome, which is an abnormal sinus tachycardia brought on by standing and relieved by recumbency, is thought to be caused by a variety of defects in autonomic modulation of the HR response to standing. Defects in norepinephrine transport and clearance, inappropriate peripheral vasoconstriction, "idiopathic hypovolemia," reduced circulating blood volume, and autoantibodies to ganglionic nicotinic Ach receptors have all been implicated in connection with postural orthostatic tachycardia syndrome.[4,6-9] In addition, primary sympathetic hyperactivity has been associated with increased angiotensin II levels in the central paraventricular nucleus, genetic factors, and in rats, hypothalamic stimulation.[10]

Secondary causes of a hyperadrenergic state are more common and are due to physiological conditions that require increased HR and vascular tone, such as CV dysfunction. Clinically, chronic left ventricular dysfunction is the most common cause of a hyperadrenergic state and an elevated resting HR; this is a detrimental compensatory mechanism for the heart to maintain cardiac output. Certainly, stress is a more frequent cause, but its effects are more difficult to assess as they are confounded by substance abuse and cigarette smoking.[11,12] Chronic activation of the sympathetic nervous system and/or limitation of parasympathetic (vagal) tone can increase the risk of CV events.[13] Conversely, increased parasympathetic tone, which occurs with regular dynamic exercise, has been demonstrated to decrease the risk of potentially lethal arrhythmias during myocardial ischemia.[14]

Maximal Heart Rate with Exercise

Many studies have evaluated maximal HR during treadmill testing in a variety of subjects, with and without CV disease (CVD). Vagal withdrawal with the initiation of exercise can result in an increase of 30 to 50 beats per minute in HR, but further increases are thought to be due to sympathetic activation. Clinically speaking, it is generally true that the higher the HR reached during the exercise test, the better the prognosis. Several factors may affect maximal HR during dynamic exercise.

Maximal HR generally declines with age, although regressions with age have varied

depending on the population studied and other factors. A consistent finding in these studies has been a relatively poor relationship between maximal HR and age. Correlation coefficients in the order of 0.40 are typical, with SDs in the range of 10 to 15 beats per minute. In general, this relationship has not been "tightened" by considering activity status, weight, cardiac size, maximal respiratory exchange ratio, or perceived exertion. An exercise program most likely has divergent effects on this relationship at the age extremes. Younger individuals may be able to achieve larger changes in cardiac dimensions than older subjects, and those larger changes may affect maximal HR. In an effort to clarify the relationship between maximal HR and age, Londeree and Moeschberger[15] performed a comprehensive review of the literature, compiling information on more than 23 000 subjects aged 5 to 81 years. Stepwise multiple regression analysis revealed that age alone accounted for 75% of the variability in maximal HR; other factors added only an additional 5% and included mode of exercise, level of fitness, and continent of origin but not sex. The 95% confidence intervals, even when accounting for these factors, ranged 45 beats per minute. Heart rates at maximal exercise were lower during bicycle ergometry than on the treadmill and even lower with swimming. In addition, trained individuals had significantly lower maximal HRs than untrained subjects.

Smoking status also affects the HR response to exercise. Smokers exhibit a lesser HR increase for a given workload than nonsmokers. In the Lipid Research Clinics study, which studied 6238 asymptomatic hypercholesterolemic white men screened between 1973 and 1976, cigarette smoking was strongly correlated to exercise performance in a dose-dependent manner. During exercise testing, the authors found that the increase in HR among smokers was lower for a given workload than that of nonsmokers.[12] The authors propose several mechanisms for this finding:

1. The aortic arch and carotid chemoreceptors of smokers become desensitized in response to long-term exposure to nicotine.[12,16]
2. Smokers who comply with instructions for abstention from tobacco before exercise testing may operate at higher oxygen carrying capacity because of carbon monoxide–induced increases in total blood hemoglobin level.[12,17,18]
3. The sharper rise in blood pressure seen in smokers may allow a higher sustained workload at a given level of myocardial oxygen consumption.[12,19]

Another factor that affects maximal HR and is also important clinically is bed rest. Among the many adverse physiological effects of bed rest are substantial increases in HR at rest and exercise.[20] The lack of gravitational forces on baroreceptor mechanisms may play a role in this accentuated HR response. Environmental hypobaric situations, such as exposure to high altitude, also cause a decreased HR response to exercise. During acute exposure to altitude, HR increases at matched submaximal workload levels and maximal workloads are decreased after prolonged exposure to altitude. Another factor that may be contributing to this effect is the reduction in sympathetic nervous system response to exercise that occurs at altitude, likely due to a reduction in β-receptor sensitivity, which underlies the reduction in maximal HR.[21]

Several factors have been demonstrated to have minimal or no effect on HR reserve. Heart rate response to exercise is affected only minimally by sex.[15] In addition, height, weight, and even lean body weight have not been shown to be independent factors affecting maximal HR.

Chronotropic Incompetence or Index/Heart Rate Impairment

Chronotropic incompetence and *heart rate impairment* are terms that have been used to describe inadequate HR responses to exercise. In a seminal study on this issue, Ellestad and Wan[22] analyzed the results from 2700 patients tested in their treadmill laboratory. They defined a group of patients who achieved below the 95% confidence limits for maximal HR regressed with age as having *chronotropic incompetence* (CI). Patients with no ST-segment depression who had CI had a 4-fold greater incidence of coronary artery disease than did those without CI in the 4 years after the test.

Subsequently, Lauer and colleagues[23] studied 146 men and 85 women who were not taking

β-blocking agents and exhibited CI defined as (1) failure to achieve 85% of age-predicted maximal HR or (2) a low *chronotropic index*, a measure that expresses HR achieved accounting for age, functional capacity, and resting HR. The patients were followed up for a mean of 41 months. Both indices were strong predictors of cardiac events (death, myocardial infarction [MI], unstable angina, or revascularization); the relative risks for failure to achieve 85% predicted HR and a low chronotropic index were just more than 2. Similar findings were made in the Framingham cohort during a 7-year follow-up among 1575 men.[24] An inadequate HR response to exercise was associated with nearly twice the risk for total mortality and cardiac events, even after adjustments were made for age and other coronary artery disease risk factors. Because the HR response to exercise reflects the balance between CNS withdrawal of vagal tone and an increase in sympathetic tone, an abnormal HR response to exercise has been hypothesized to be related to abnormal autonomic balance.[25] However, it is vital to recognize that the measurement of chronotropic incompetence may in part reflect the inability of end organs such as the heart to respond appropriately to normal ANS input rather than ANS dysfunction.

A larger cohort study conducted by Jouven and colleagues[26] followed up 5713 asymptomatic working men for a mean period of 23 years after exercise testing. Subjects who had an increase in HR less than 89 beats per minute during exercise testing were found to have a relative risk of sudden death from MI of 4 after adjusting for confounding factors. This was a stronger prognostic factor than resting HR or HRR but had little association with nonsudden death from MI. Here, the authors conjecture that autonomic imbalances may *precede* the symptoms of CVD and aid in the early identification of patients who are at risk for sudden death. Furthermore, these findings support the suggestion that autonomic imbalance, as revealed during exercise testing, might be associated with the development of lethal arrhythmias.[13,26,27]

A recent study by Falcone et al. suggests that the timing of the heart rate response to exercise is vital. Their work demonstrated that an excessive heart rate response during the first minute of exercise appears to predict adverse CV events in patients with coronary artery disease.[71] The kinetics of the heart rate response to exercise likely reflects the timing of vagal (parasympathetic) withdrawal and sympathetic escalation and seems to offer further insight into the autonomic balance during exercise. The identification of preexisting autonomic imbalance in patients with no manifestations of CVD indicates that there is a subset of healthy patients who have a normal autonomic response to exercise, as well as a subset of patients with an abnormal response to exercise who are currently healthy but are predisposed to sudden cardiac death. Likewise, in the subset of the population that presently has CVD and is at a higher baseline risk of cardiac events and death, there may be a superimposed increase in risk of such events from an arrhythmogenic autonomic imbalance. We may, then, stratify the risk of death from CV events, as identified by the autonomic response to exercise, by dividing the population into 4 groups:

1. Healthy patients with a normal CV response to exercise;
2. Otherwise healthy patients with an abnormal autonomic response to exercise who have increased risk for lethal arrhythmias;
3. Patients with CVD who have a normal autonomic response to exercise but increased risk of nonsudden death from MI or other nonsudden CV events and moderately increased risk of sudden cardiac death due to the presence of CVD;
4. Patients with CVD and an abnormal autonomic response to exercise who have a greatly increased risk of sudden cardiac death and nonsudden cardiac death from autonomic imbalance and CVD (Fig 2).

We might consider that the risk for sudden cardiac death due to autonomic imbalance, as indicated by the CV response to exercise, and risk of sudden and nonsudden cardiac death from CVD are relatively independent. We propose that a simple sum of the 2 might, then, serve to quantify the risk of death from *all* cardiac events, both sudden and nonsudden:

$$RR = RR_{ANS} + RR_{CVD} \quad (a)$$

where RR is the total risk of death from all cardiac events relative to a population with

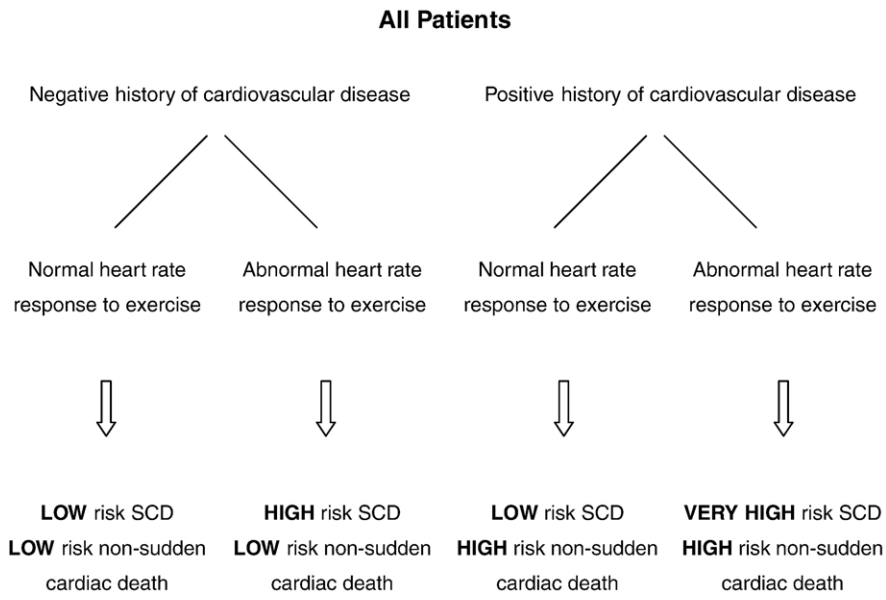

Fig 2. Schematic method for stratifying CV risk by degree of autonomic imbalance and CVD status. Abbreviation: *SCD*, sudden cardiac death.

normal HR response to exercise and no CVD, RR_{ANS} is the risk of sudden death relative to the population with normal HR response to exercise, and RR_{CVD} is the risk of cardiac death (both sudden and nonsudden) relative to the population with no CVD.

Heart Rate Recovery

Recovery from a dynamic exercise test involves reactivation of the parasympathetic system and deactivation of sympathetic activity, causing a decline in HR. Investigations aiming to quantify HRR have calculated time constants by fitting HR decay data to several mathematical models.[28–32] Alternatively, most investigators have simply measured the change in HR from peak exercise to minute 1 or 2 of recovery or considered the slope of the decline. Numerous recent investigations have observed that the rate at which the HR recovers from exercise at 1 or 2 minutes powerfully predicts prognosis, with slower HRR rates portending a significantly higher risk of death.

Early recovery is dominated by parasympathetic reactivation, with sympathetic withdrawal becoming more important later in recovery.[33] In a pharmacologic blockade study, Imai et al[28] computed HRR decay curves using beat-to-beat data and concluded that short- and moderate-term HRR curves are vagally mediated because HR decay 30 seconds and 2 minutes into recovery was prolonged with atropine and dual blockade; however, the HR decay for 2 minutes was more prolonged with dual blockade than with atropine alone, indicating that later recovery also depends on sympathetic modulation. This conclusion was also supported by the observation that plasma norepinephrine concentrations during the first minute of recovery remain constant or even increase immediately after exercise.[34]

Interestingly, smoking also affects HRR after exercise. In the Lipid Research Clinic study described earlier, Gordon et al[12] demonstrated that HRR after exercise testing was significantly affected by smoking status in a linear, dose-dependent fashion. The decline to baseline HR after submaximal exercise was slower in smokers than in nonsmokers.

Heart Rate Recovery—The Curve

Measuring HR precisely at a moment in time, during the often chaotic variability of recovery, seems imprecise. Conceptually, a functional curve fit to a given HRR period offers the potential to both minimize the error associated

with a single estimate and leverage information that may be contained in the overall shape of the curve. Previous investigators have proposed an exponential curve of the general form

$$\mathrm{HRR} = \mathrm{HR_{Rest}} + (\mathrm{HR_{Peak}} - \mathrm{HR_{Rest}})e^{-kt} \quad \text{(a)}$$

to characterize the recovery process.[28] The term HR_{Peak}-HR_{Rest} is the HR reserve. As discussed above, an age-adjusted low value of this parameter (ie, chronotropic incompetence) has been shown to predict the risk of CV events and mortality, with higher peak HR indicating lower risk. The decay coefficient k controls the rate of decay of the curve, from peak HR through recovery, and t is time measured from the peak HR in minutes. Larger values of k result in a more rapid return to the resting HR baseline. This functional form may be fit to the recovery data, either at distinct points in time (eg, peak, 1, 2, 3, and 5 minutes) or continuously for beat-to-beat estimates of HR.

There are 2 noteworthy considerations that arise when fitting Eq. (a) to HRR data or when comparing clinical results between different investigators. First, the start of recovery is often difficult to pinpoint. Some investigators use a cool-down walk for the entry into recovery, whereas other investigators attempt to transition patients to a supine position immediately. To maximize stroke volume and provide a consistent basis for comparison, we recommend transitioning the patient as quickly as possible to a supine position. However, even with this methodological goal, depending upon patient mobility and test protocol, there may be a transition period of 10 to 30 seconds when the patient is only partially in recovery. This time interval is a large fraction of the typical 1 to 2 minute post exercise interval commonly used in measuring HRR and undoubtedly introduces uncertainty into the metric.

The second vital consideration is that resting HR is a dynamic variable. It is fairly common to observe that the HR in recovery decays asymptotically to a value distinctly different that the initial resting rate before the test, sometimes with differences as large as 10 to 20 beats per minute. Given normal HR variability, forcing the HRR curve to return to a pretest value of the resting HR can introduce systematic bias in the derived value of k.

These considerations lead to a proposed modified form to describe the HRR curve:

$$\mathrm{HRR} = \mathrm{HR_{Rest}} + \left(\mathrm{HR_{Peak}} - \mathrm{HR_{Rest}}\right) \cdot e^{-k(t-t_0)} \quad \text{(b)}$$

where the parameters $\mathrm{HR_{Rest}}$, k *and* t_0 (the effective time delay for the start of recovery) are simultaneously derived through a least squares fit to the HRR data. Our group has found that this formulation, fit to 15-second median estimates of HR, for recovery periods of 5 or more minutes in duration (ie, 20 or more simultaneous equations solved for 3 unknowns), provides a stable and robust estimate of HRR, corrected for the transition into recovery time and posttest resting HR. An example of this can be seen in Fig 3. In a population of 1959 patients, the average SD of the curves fit to the 15-second median averages was less than 2.4 beats per minute, suggesting that form (b) does an excellent job of capturing the shape of the HRR curve (we are currently assessing the parameters derived from form [b] for risk stratification for CV events and mortality).

Heart Rate Recovery and Prognosis

The rate of HRR post exercise is theorized to be due to high vagal tone, and recent evidence has demonstrated its value as an independent predictor of prognosis. Cole et al[35] studied 2428 adults who had been referred for exercise nuclear perfusion scans. In univariate analysis, they found that a drop in HR of 12 beats per minute or less at 1 minute after peak exercise was associated with a relative risk of 4.0 for death from any cause over a 6-year period. After adjustments were made for age, sex, the use or nonuse of medications, the presence or absence of myocardial perfusion defects on thallium scintigraphy, standard cardiac risk factors, the resting HR, the change in HR during exercise, and workload achieved, a low value for HRR remained predictive of death (adjusted relative risk, 2.0; 95% confidence interval, 1.5-2.7; $P < .001$).

These investigators then studied 5234 asymptomatic patients enrolled in the Lipid Research Clinics Prevalence Study.[36] These patients underwent exercise testing using a Bruce protocol, and tests were stopped when 85% to 90% of peak HR was achieved. There was no cool down walk

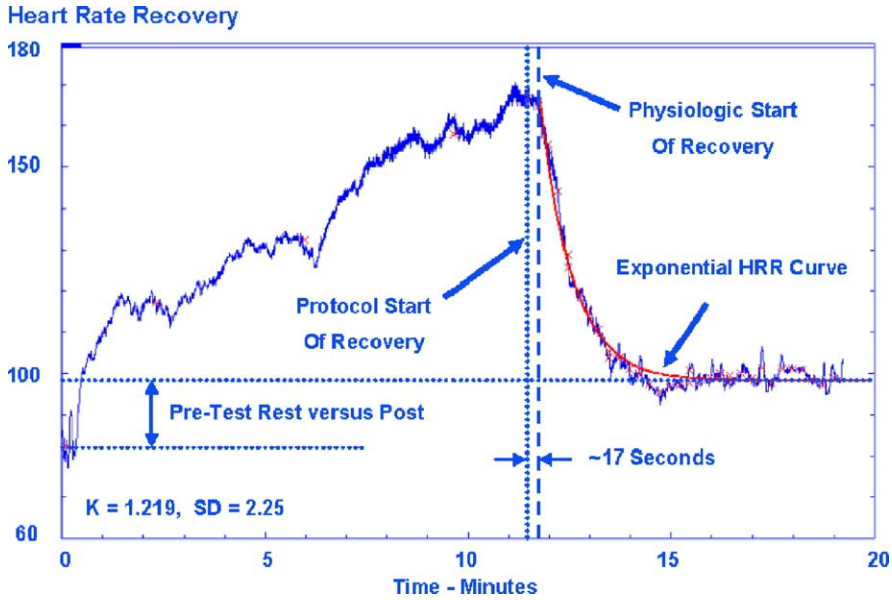

Fig 3. Sample heart rate recovery curve. The exponential decline of the recovery curve begins later than both the peak HR and the end of the exercise phase of the test. The HR recovers to an effective resting rate that is distinct from the pretest value. The SD of the exponential curve, fit to the 15 seconds median HR averages ("X" along the curve), is 2.25 beats per minute.

and HRR was measured after 2 minutes of recovery. Heart rate recovery continued to be a strong predictor of all-cause mortality; patients with an abnormal value had a mortality rate of 10%, whereas patients with a normal value had a mortality rate of 4% at 12 years of follow-up (relative risk, 2.58; confidence interval, 2.06-3.20). After adjustment for standard risk factors, fitness, and resting and exercise HRs, abnormal HRR remained predictive of mortality (adjusted relative risk, 1.55; confidence interval, 1.22-1.98) ($P < .001$). These investigators then published another study using patients referred for standard treadmill testing, which again demonstrated the ability of HRR to predict all-cause mortality, although notably, the cut-off value for an abnormal test was different.[37] It is important to note, however, that CV mortality was not evaluated in these studies. We acknowledge that there is strong evidence demonstrating the inaccuracy of death certificates about attributing death due to CV causes. However, the goal of cardiac testing is to predict CVD (rather than other life-threatening disease states such as cancer) so that decisions regarding CV interventions can be made. This is in contrast to outcome studies evaluating CV interventions, for which all-cause mortality is the more appropriate outcome measure. Thus, we believe that CV mortality (in addition to all-cause mortality) must be evaluated as an outcome in any study of cardiac testing measures.

Therefore, we attempted to validate the use of HRR for prognosis in a male veteran population referred for exercise treadmill testing, evaluating both all-cause mortality and CV mortality.[38] The all-cause mortality rate in our study was higher than in previous studies, but we found that an HRR less than 22 beats per minute at 2 minutes post exercise identified a group of patients at high risk for all-cause death in both univariate and multivariate analysis. β-Blockers had no significant impact on this relationship, and similar to Cole et al,[35] we found that low exercise capacity was the most powerful predictor of all-cause mortality. For CV mortality, HRR was univariately predictive, but when entered in a multivariate Cox hazards model, HRR was not a significant predictor of CV death. These findings indicated that HRR is more predictive of non-CV than CV mortality. This is consistent with studies showing the inability of HRR to predict angiographic disease and should be considered when the exercise test

is used to determine the appropriateness of cardiac interventions.

A distinct advantage of this study is that our patient population also underwent coronary angiography. This made it possible to evaluate the diagnostic ability of HRR for coronary disease. Surprisingly, HR in recovery was not selected among the standard variables to be included in a logistic model and its receiver operating characteristic curve did not indicate any discriminatory value. Thus, although HRR has been validated as an important prognostic variable for all-cause mortality, it did not help diagnose coronary disease.

To further define the prognostic significance of HRR, Jouven et al[26] evaluated the ability of HRR to predict sudden death. In a cohort of 5713 asymptomatic working men followed up for 23 years, those with a low HRR had more than twice the risk of sudden death. Interestingly, risk of nonsudden cardiac death was not different between quintiles of HRR. The finding that a lower HRR after exercise testing is associated with a lower risk of sudden cardiac death, but not lower risk of nonsudden cardiac death, indicates that it may be valuable in the prediction of superimposed risk of sudden cardiac death in patients with or without other signs of CVD.

Later studies addressed the issues of the ability of HRR to predict CVD/events rather than all-cause mortality and its performance in women and patients with diabetes. Morshedi-Meibodi et al sought to demonstrate the association of HRR after exercise with the incidence of coronary heart disease (CHD) and CVD by evaluating 2967 Framingham study subjects (1400 men; mean age, 43 years) free of CVD over a 15-year follow-up period.[39] In multivariate analysis, continuous HRR indexes were not associated with the incidence of CHD or CVD events or with all-cause mortality. However, in models evaluating quintile-based cut points, the top quintile of HRR (greatest decline in HR) at 1 minute after exercise was associated with half the CHD and CVD as the bottom quintile. Interestingly, this quintile approach still did not predict all-cause mortality, contradicting the findings of earlier studies in asymptomatic patients.

Studies of female subjects have indicated associations between HRR after exercise and outcome. A total of 2994 asymptomatic women without CVD, 30 to 80 years of age, performed a near-maximal Bruce-protocol treadmill test as part of the Lipid Research Clinics Prevalence Study (1972-1976).[40] They were followed for 20 years with CV and all-cause mortality as the end points. There were 427 (14%) deaths of which 147 were due to CV causes. Low HRR was independently associated with increased all-cause and CV mortality.

Faster HRR after exercise has also been associated with decreased risk of CV death in diabetic male patients. In a cohort study, Cheng et al examined 2333 male patients with diabetes who underwent treadmill testing at the Cleveland Clinic.[41] During 15 years of follow-up, there were 142 deaths that were considered CVD-related and 287 total deaths. In multivariate analysis comparing the highest and lowest quartiles for HRR, the hazard ratio was 1.5 to 2 for CV death after adjustment for age, metabolic equivalents (METs), resting HR, fasting blood glucose, body mass index, smoking, alcohol consumption, lipids, and history of CVD.

Thus, there is a large body of evidence that has demonstrated the value of HRR as an independent predictor of all-cause and CV mortality. However, the relative prognostic value of this variable compared with other measures from the standard exercise test and the value of HRR for diagnosing cardiac disease remains unclear.

Heart Rate Variability

Beat-to-beat variations in the R-R interval on the electrocardiogram, measured over a period ranging from a few minutes to 24 hours, are known as HRV. Heart rate variability is thought to represent the autonomic balance between the sympathetic and parasympathetic pathways acting on the intrinsic rhythm of the sinoatrial node of the heart.

A variety of methods have been devised to quantify HRV, ranging from simple statistical descriptors to complex nonlinear mathematical algorithms. Most commonly, HRV has been expressed as time and frequency domain components. Time domain indices are the simplest to calculate. The most commonly used indices of HRV simply use statistics derived from the

intervals between R-R complexes on the electrocardiogram. For example, the SD of all the R-R intervals in a given period, expressed in milliseconds, is referred to as SDNN. Because most systems attempt to exclude abnormal beats such as premature ventricular contractions and, to some extent noise, "NN" refers to normal-to-normal intervals or adjacent beats originating from the sinus node. Another common interval-based measure, SDANN, expresses the SD of the average of R-R intervals over each 5-minute period and is generally thought to represent variation due to circadian rhythms. Other time domain techniques use statistics calculated from differences between successive beat to beat intervals. These include pNN50 (the percentage of adjacent R-R intervals that are >50 milliseconds apart) and rMSSD (the root mean square of the differences in the differences in adjacent R-R intervals). The latter 2 indices are based on differences between successive R-R intervals and are generally thought to reflect vagal modulation of the sinoatrial (SA) node. Table 3 shows the most frequently used time domain HRV measurements and their definitions.

The second method of assessing HRV is by the use of power spectral analysis or frequency domain analysis. Power spectral analysis plots the distribution (spectra) of HR oscillations in the frequency domain by mathematically transforming sequential R-R intervals on the electrocardiogram into specific frequency components. The major mathematical technique is the Fourier transform algorithm which can plot the relative energy of different frequency components of HRV. The Fourier transform is based on the Fourier theorem, which states that any periodic signal can be expressed as a sum of an infinite set of sine and cosine functions with different characteristic periods of oscillation and different weighting coefficients. The Fourier transform projects the complex periodic oscillation in R-R interval onto each of these periodic basis functions in much the same way that vectors in 3 dimensional space are projected onto the 3 basis vectors that define our visual space. The relative power of each point in the frequency domain subsequently can be obtained. Heart rate cycles are identified as HF (0.15-0.40 Hz corresponding to 9 to 24 oscillations per minute); LF (0.04-0.15 Hz—2.4-9 oscillations per minute); very LF (VLF, 0.0033-0.04 Hz—0.2-2.4 oscillations per minute); and Ultra Low- Frequency (ULF, below 0.0033—0.2 oscillations per minute). The VLF peak is generally quoted in absolute units and as a percentage of total power (the total area under the HRV spectrum curve), whereas or although the LF and HF peaks are usually quoted in absolute units, as a percentage of total power, and in units that are normalized to total power (after subtracting the contribution of the VLF component). Fig 4 illustrates the frequency domain components and their possible significance, and Table 4 lists these components and their respective frequency and power characteristics.

Heart rate variability has been evaluated in a variety of conditions although hereditary aspects have rarely been considered.[42] Multiple recent studies have demonstrated the ability of HRV measures at rest to predict fatal arrhythmias and death due to cardiac causes, raising great interest in the field. Reduced resting HRV has been associated with higher risk of fatal arrhythmias and death due to cardiac causes. These observations have been made among elderly subjects,[43] patients with diabetes,[44] patients after an MI,[45,46] those with chronic heart failure,[47-51] as well as other conditions.[52-56] Although the mechanism for this association has not been firmly established, several hypotheses have been proposed.

Table 3. Time Domain Heart Rate Variability Measurement

Parameter	Definition	Normal values (±SD)
SDNN	SD of all R-R intervals	141(± 39 milliseconds)
SDANN	SD of the averages of 5-min segments	127(± 35 milliseconds)
SDNN index	Mean of the SD s for 5-min segments	
RMSSD	Square root of the mean of the sum of squares of differences between adjacent R-R intervals	27(± 12 milliseconds)
NN50 count	No. of pairs of adjacent R-R intervals differing by more than 50 milliseconds	
pNN50	NN50 count divided by the no. of R-R intervals >2%	

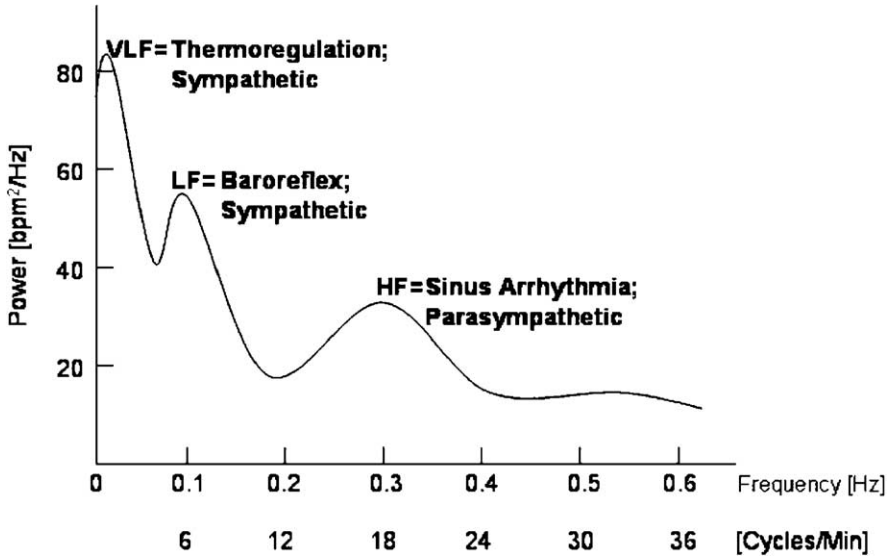

Fig 4. The frequency domain components of HR variability are illustrated.

Altered CV neural regulation expressed by higher HRV may reflect underlying subclinical disease, thus predisposing an individual to higher mortality. Reduced HRV may be a reflection of elevated sympathetic activity[47,57]; among other things, an elevation in sympathetic activity is known to attenuate baroreceptor reflexes, which presumably decreases the threshold for ventricular fibrillation, predisposing an individual to life-threatening arrhythmias.[3,27] Lower HRV may also reflect an intrinsic impairment in the physiological regulatory and adaptive mechanisms that regulate HR, causing the individual to be less able to tolerate a perturbation such as an ischemic event or more routine rhythm disturbances. Data from animal studies have supported this idea by demonstrating that autonomic regulation plays an important role in the occurrence of life-threatening arrhythmias during experimentally induced cardiac or cerebral ischemia.[58]

High-Frequency HRV—The Respiratory Component

The pulmonary center in the brain stem blocks vagal activity to the lungs during inspiration to cause bronchodilation and facilitate breathing. There is cross talk with the cardiac center resulting in an increase in HR during inspiration. This results in a relative high frequency (HF) oscillation in HR timed with inspiration at a rate of approximately 12 cycles per minute. This has been termed *HF HRV* and is measured by the degree of variability of R-R intervals. It can be noted as "sinus arrhythmia" on a routine ECG and is generally thought to reflect strictly efferent vagal influences. Interestingly, although baroreflex sensitivity and HF power are both measures of parasympathetic activity, these 2 measures poorly correlate, indicating that they do not yield identical information.[59]

Table 4. HRV Spectral Analysis Components

Name	Frequency range	Theoretic physiology	Normal power
HF bands	0.15-0.40 Hz	Respiration; parasympathetic	150 ± 70 (milliseconds^2)
LF bands	0.04-0.15 Hz	Baroreflex; sympathetic discharge	140 ± 130 (milliseconds^2)
VLF bands	0.0033-0.04 Hz	Thermoregulation; sympathetic discharge	Variable
Ultra LF bands	up-0.0033 Hz	Unknown	Variable
LF/HF ratio			1.2 ± 1

Low-Frequency HRV

Two other oscillations of HR are noted to occur less frequently than respiration, an LF component and a VLF component. The significance of these oscillations is not clear, but they are generally thought to estimate sympathetic cardiac modulation, although some investigators suggest they reflect both vagal and sympathetic tone. These components may represent sympathetic discharges to baroreceptors to maintain consciousness during hemodynamic collapse or thermoregulatory sympathetic discharges to protect from hypothermia, both of which impart a clear survival advantage in the context of human evolution. The ratio of LF to HF energies is thought to provide an estimate of the ANS balance at rest.[60]

There is evidence that prevalent LF HRV (the frequency at which the dominant LF peak occurs) is a significant independent predictor of mortality in post-MI patients.[61] In general, there are 2 competing theories regarding the prognostic value of LF HRV: the central oscillator theory, which supports the prognostic value of spectral analysis, and the baroreflex feedback loop theory, which does not support spectral analysis-based prognosis. Malpas[62] reviewed recent research examining the origin of variability associated with LF oscillations and proposed a new hypothesis to account for LF variability; he argues that the vascular response to sympathetic activity may help determine the strength of oscillations. Although HRV was previously thought to reflect autonomic tone, he concludes that there are additional nonbaroreflex and nonautonomic pathways that may affect the R-R interval. This new hypothesis would weaken the rationale for using spectral analysis for estimating arrhythmic risk but does not negate it.

Heart Rate Variability During Exercise

The LF/HF ratio has been commonly accepted to be a reflection of sympatho/vagal balance. However, spectral analysis of patients during exercise testing has shown that HRV does not exhibit the expected LF/HF ratio, consistent with sympathetic hyperactivity during exercise and parasympathetic drive during recovery. Early spectral analysis studies of HRV data during exercise seemed to indicate that HF power decreased during exercise. However, these studies also showed total power declining in the same period. Thus, studies quantifying HF and LF power in normalized units, which allow a better appreciation of the fractional distribution of HRV energy, are more illuminating. Normalized HF power, which is generally thought to be an indicator of vagal activity, would be expected to diminish during exercise. Rather, it increases gradually during exercise, whereas normalized LF power, which is thought to reflect sympathetic activity, decreases during exercise in most studies.[63-66] Interestingly, preliminary results of a study of HRV data from 1297 male veterans exercise-tested between 1997 and 2004 at Palo Alto Veterans' Affairs Hospital indicate that normalized LF power is greater in the 2-minute period immediately after exercise testing than in the last 2 minutes of exercise. Equally anomalously, normalized HF power was found to be lower in the recovery period, when vagal tone is highest, than in the last 2 minutes of exercise. It seems then, that additional mechanisms, such as baroreceptor function, must also account for HRV during exercise or that an alternative interpretation of the effects of autonomic function on HRV during exercise is needed. It must be remembered that the spectral density of each of the peaks found in the HRV spectrum represents only the amount of periodic modulation of beat-to-beat interval about a certain mean value. Thus, during exercise testing in which the CV response to constant sympathetic input results in a steady increase in HR, and during initial recovery in which the HR is slowed by vagal tone, a decline in the periodic nature of these peaks and, thus, their spectral density, might actually be expected. These findings suggest that HRV is probably best explained by the complex interplay of multiple inputs to the heart, rather than simply autonomic imbalance.[62,67]

Our group is currently investigating the prognostic value of time domain and frequency domain measures of HRV data derived from exercise ECGs. The value of the exercise test as a prognostic tool would be greatly augmented by the addition of this novel predictive measure.

Conclusions

The ANS and CV Mortality

The complex interaction between the ANS and the CVS has recently garnered great interest. There is growing evidence that several measures of this interaction are independent predictors of adverse CV events. Whether these measures reflect a primary abnormality of the ANS or a pathological end organ response to normal ANS input remains to be elucidated. Traditional prognostic factors such as age, lipid profile, smoking status, and family history will certainly continue to be important to the prediction of risk for developing CVD and risk of CV events. However, markers of autonomic interplay with the CVS may become more important in the determination of risk for mortality and particularly sudden cardiac death both in patients with and those without known CVD.

Heart Rate Reserve and Heart Rate Recovery in Exercise

Exercise testing with measurements of HR reserve and HRR can serve as a simple method for assessing the effects of autonomic function on the CV response to exercise. These markers, which have previously been thought to be surrogate markers for fitness, are now accepted as independent predictors of mortality. Ongoing research will be vital in demonstrating the most precise and prognostically significant measurement methodologies for these exercise parameters.

Heart Rate Variability

Heart rate variability has become an area of great interest in the past few years to both physiologists and clinicians interested in finding new prognostic markers for cardiac death. There is strong data demonstrating the prognostic value of HRV at rest in a variety of conditions, and HRV with exercise is currently being investigated. There is also a growing body of evidence examining the prognostic value of the various time domain and spectral domain components of HRV both at rest and with exercise. Heart rate variability components seem to yield particular insight into the autonomic balance between parasympathetic and sympathetic influences on the CVS. These components may therefore prove to be an especially powerful prognostic tool for CVD.

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