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Autonomic function and prognosis

ABSTRACT

Autonomic nervous system function is assessed in the clinic by measuring resting heart rate, heart rate variability, or heart rate recovery following exercise. Each of these measures is a strong predictor of cardiovascular risk and all-cause mortality in primary and secondary prevention settings. These measures have been used to identify correlates of autonomic nervous system dysfunction at both the patient level (eg, obesity, diabetes, heart failure) and the environmental level (eg, smoking, social stress, air pollution). Future research must determine how to exploit the associations between autonomic system dysfunction and poor prognosis to improve patient outcomes.

First-year medical students are well aware that the autonomic nervous system regulates heart rate and blood pressure along with respiratory and digestive functions. The past 10 to 20 years have seen increased appreciation of the medical relevance of the the autonomic nervous system beyond first-year physiology examinations; even mild disturbances of autonomic nervous system function predict materially worse prognosis.[1–3] Researchers have focused on the use of readily available measures, such as heart rate,[4] heart rate variability,[5] and heart rate recovery,[6] to link autonomic nervous system dysfunction with mortality and morbidity.[1] In addition, epidemiologists have exploited these tools to identify correlates of autonomic nervous system dysfunction at patient and environmental levels.[7] Although it is not yet known how best to incorporate autonomic nervous system measures into routine clinical care, there is increasing excitement about the insights that this work has revealed.

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MEASURES OF AUTONOMIC NERVOUS SYSTEM FUNCTION

Although many measures of autonomic nervous system function have been described, three relatively straightforward approaches are based on heart rate.[1]

Resting heart rate is the simplest to obtain, as it does not require any special technology. People with high levels of parasympathetic nervous system tone have lower resting heart rates, as is typically seen in world-class athletes. Conversely, conditions characterized by increased levels of sympathetic tone manifest as sinus tachycardia; classic examples include congestive heart failure, anemia, and hypovolemia.

Heart rate variability. Even before the advent of the electrocardiogram, it was known that heart rate normally varies with respiration.[8] Physiologic sinus arrhythmia can be easily demonstrated by plotting heart rate over time in resting supine subjects, typically yielding a tracing characterized by high-frequency, low-amplitude waves. When a normal subject assumes an upright position, the resting heart rate increases and there is an increased absolute amount of variability, but the frequency of the variability wave decreases. Using Fourier transform techniques, one can translate the amplitude and frequency of the waves shown in the top plot of **Figure 1** into power domain functions, as shown in the bottom plot of **Figure 1**.[8] Heart rate variability functions can be divided into high-frequency, low-frequency, and very-low-frequency domains.[8,9] The high-frequency peak, which is reflective of the very fine variability seen with respiration at rest, is thought to reflect parasympathetic nervous system tone. The low-frequency and very-low-frequency peaks are thought to reflect mixed effects of parasympathetic tone and sympathetic tone.

Heart rate recovery. Heart rate variability measures require continuous Holter monitoring as well as sophisticated software. The numerous types of heart rate variability measures are not intuitive for most clinicians. Exercise heart rate recovery is an arguably more straightforward method of assessing parasympathetic tone.[1] During a graded exercise test, heart rate increases as a result of withdrawal of parasympathetic

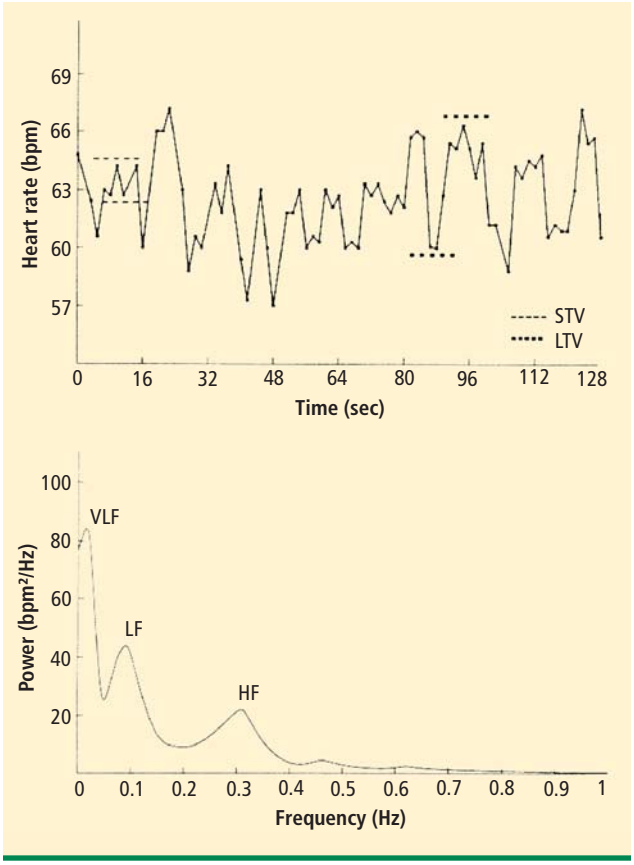

FIGURE 1. Example of time-domain measures of heart rate variability (STV = short-term variability; LTV = long-term variability). The top plot shows heart rate as a function of time. In the bottom plot, Fourier transform yields power values of very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF) domains. The high-frequency domain is thought to reflect parasympathetic tone, whereas the very-low-frequency and low-frequency domains are thought to reflect a mixture of parasympathetic and sympathetic tone.

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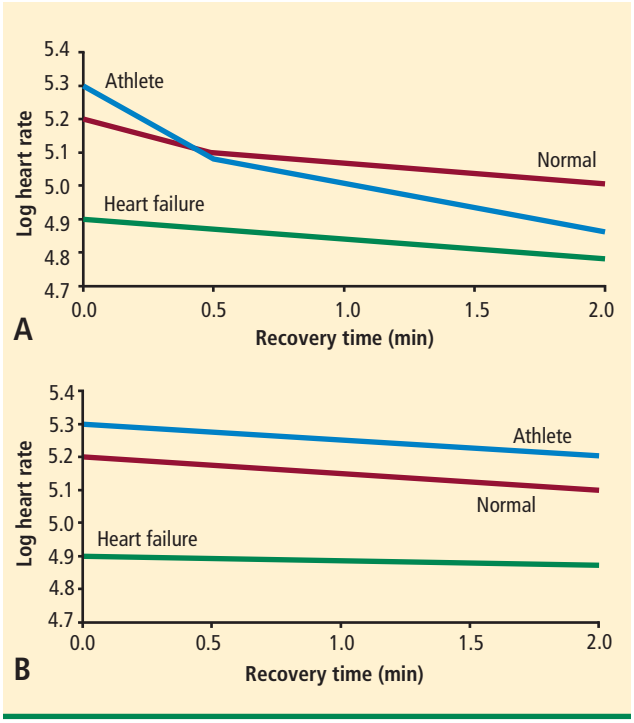

FIGURE 2. Demonstration of the association between parasympathetic tone and heart rate recovery. **(A)** Absolute heart rates (after logarithmic transformation) are shown during the first 2 minutes after exercise in three groups of subjects. Among athletes and normal subjects, there is a biexponential relationship. **(B)** Postexercise absolute heart rates are shown again, this time after administration of atropine, in which case the initial steep slope disappears. Figure is based on data from Imai et al.[10]

tone and increased sympathetic tone. During the first 30 seconds after exercise, heart rate decreases quickly, mainly because of rapid reactivation of the parasympathetic nervous system.[10]

The association between early heart rate recovery and parasympathetic nervous system function was demonstrated elegantly by Imai and colleagues in a study of three groups of subjects—athletes, normal subjects, and patients with heart failure.[10] Among athletes and normal subjects there was a biexponential pattern of heart rate during early recovery, with a steep log-linear decrease during the first 30 seconds followed by a more shallow decline **(Figure 2A)**. When the same subjects were given atropine and exercise testing was repeated, the initial steep decrease in heart rate observed among athletes and normal subjects disappeared **(Figure 2B)**. The authors concluded that early heart rate recovery is primarily a manifestation of parasympathetic reactivation.

AUTONOMIC NERVOUS SYSTEM FUNCTION AND MORTALITY

Resting heart rate

There is a remarkably strong association between heart rate and survival, an association that transcends species.[4] Small mammals that have rapid heart rates have short life expectancies. Larger mammals that have slower heart rates have correspondingly higher life expectancies. Among nearly all mammals, life expectancy is close to 1 billion heartbeats.

Investigators have been able to increase survival in animal models by deliberate slowing of heart rate. An experiment performed in mice more than 30 years ago showed that life expectancy increases with low-dose digoxin, a parasympathomimetic agent.[11] More recently, a mouse model has been used to show that ivabradine, a sinus node ion channel blocking agent that specifically reduces heart rate without affecting

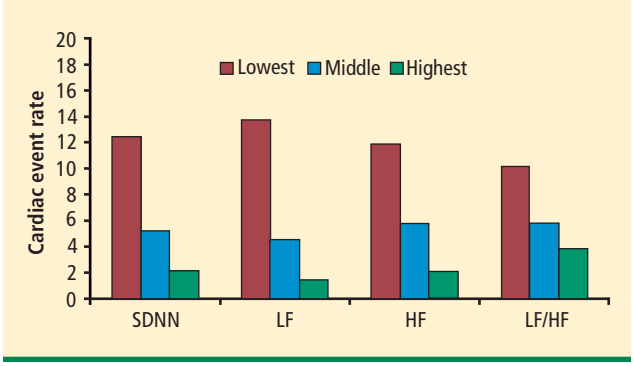

FIGURE 3. Association between measures of heart rate variability and cardiac events in the Framingham Heart Study. Each measure is divided into tertiles from lowest to highest (SDNN = standard deviation of R-R intervals of normal beats; LF = low-frequency power; HF = high-frequency power; LF/HF = ratio of LF power to HF power). Figure is based on data from Tsuji et al.[16]

vascular tone, inhibits development of atherosclerosis in genetically susceptible knockout mice.[12]

There is an extensive epidemiological literature linking heart rate to mortality in large human populations.[4,13] As heart rate increases to 75 to 80 beats per minute, there are marked increases in total mortality and mortality due to coronary heart disease. As is well known, administration of beta-blockers reduces mortality in survivors of myocardial infarction. What is particularly remarkable is that the magnitude of reduction in mortality with beta-blocker therapy is directly proportional to the magnitude of heart rate decrease.[14] In a recent analysis of hypertensive patients enrolled in a large-scale randomized trial, a strong association was noted between mortality and increasing heart rate at the time of randomization as well as after treatment with either verapamil or a beta-blocker.[15]

Heart rate variability

Just as with resting heart rate, there is a robust literature linking decreased heart rate variability to cardiac events and mortality. Among healthy elderly subjects enrolled in the Framingham Heart Study, decreased heart rate variability was associated with a substantially increased likelihood of major cardiac events **(Figure 3)**.[16] The Framingham investigators measured the standard deviation of R-R intervals that do not include ventricular ectopic beats (SDNN) as well as time-domain measures. Lower values of the ratio of low-frequency power to high-frequency power, which would correspond to lower levels of parasympathetic tone, were also associated with increased mortality. Similarly, among survivors of myocardial infarction, especially those with low ejection fractions, decreased heart rate variability predicted substantially higher mortality rates.[5,17,18]

Heart rate recovery

In 1999, Cole and colleagues reported on the association between heart rate recovery during the first minute after exercise and all-cause mortality in approximately 2,400 patients who were candidates for first-time coronary angiography.[6] An abnormal heart rate recovery was defined as a reduction from the peak heart rate of 12 beats per minute or less, which corresponded to the lowest quartile. Thus, a patient achieving a peak heart rate of 160 beats per minute would be considered to have an abnormal heart rate recovery if 1 minute later the heart rate was 148 beats per minute or higher. Patients who had an abnormal heart rate recovery had a nearly fourfold increased risk of all-cause death; even after adjusting for numerous confounders, including exercise capacity, there was still a twofold independent increased risk of death. This initial observation has since been confirmed in other cohorts.[19,20] The link between heart rate recovery, mortality, and cardiovascular prognosis appears to be independent of symptom status,[21] type of recovery protocol,[22] left ventricular ejection fraction,[22] and angiographic severity of coronary artery disease.[23]

The mechanism by which an abnormal heart rate recovery predicts increased mortality is unclear. Given that heart rate recovery is thought to reflect parasympathetic nervous system function, and given that increased parasympathetic tone is believed to have antiarrhythmic effects, one might hypothesize that lower heart rate recovery would predict sudden cardiac death. In 2005, investigators from the Paris Civil Service Study reported on the association of exercise heart rate recovery and type of mortality; low heart rate recovery was strongly predictive of sudden cardiac death but not of non-sudden cardiac myocardial infarction death.[20] A separate study from the Cleveland Clinic showed that among more than 29,000 patients, frequent ventricular ectopy during early recovery was strongly predictive of death, whereas frequent ventricular ectopy during exercise was not.[24] These two studies together suggest that the link between heart rate recovery and mortality may be a reflection of the antiarrhythmic properties of the parasympathetic nervous system.

It is well known that there is an exceptionally powerful link between functional capacity and cardiovascular risk.[25,26] People who are in excellent physical shape have high levels of parasympathetic tone. Among patients with suspected coronary artery disease, there is a strong dose-response relationship

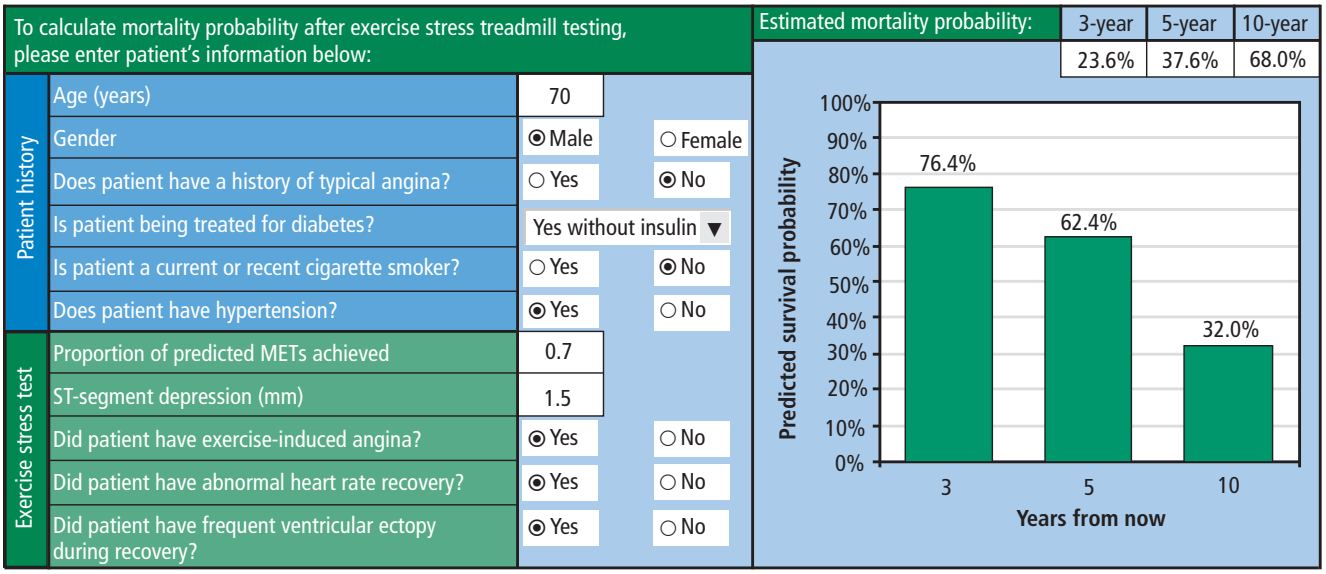

FIGURE 4. User interface of an externally validated mortality prediction model for primary prevention patients with normal electrocardiograms undergoing exercise testing.[27] This prediction model includes easily obtained cardiovascular risk factors as well as measures of autonomic function.

between heart rate recovery and physical fitness.[6] While the link between functional capacity and prognosis is complex, it is conceivable that parasympathetic protection against arrhythmias and shear-induced plaque rupture may play a role.

Both heart rate recovery and functional capacity are easy to measure using standard exercise test equipment. Recently, investigators from the Cleveland Clinic and Kaiser Permanente derived and externally validated a simple multivariable instrument by which all-cause mortality can be predicted in subjects with a normal electrocardiogram and no history of coronary disease.[27] This instrument includes measures of functional capacity, heart rate recovery, and frequent ventricular ectopy during recovery. An example of the user interface is shown in **Figure 4**.

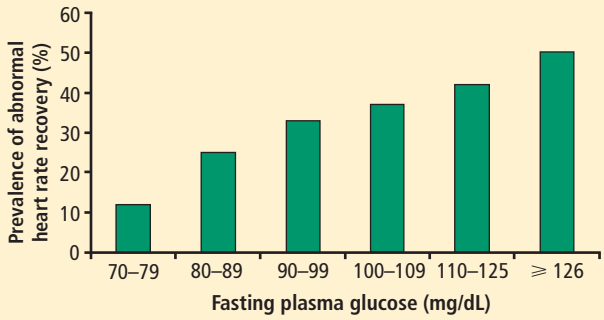

FIGURE 5. Association of fasting plasma glucose with abnormal heart rate recovery among healthy subjects enrolled in the Lipid Research Clinics observational cohort study.

DETERMINANTS OF AUTONOMIC NERVOUS SYSTEM FUNCTION

There is an extensive literature documenting a number of determinants of autonomic tone.[3,7] On a patient level, decreased levels of parasympathetic tone or increased levels of sympathetic tone have been linked to obesity, insulin resistance, diabetes, hypertension, hypercholesterolemia, depression, anxiety, heart failure, and peripheral vascular disease.[3]

The association between diabetes and autonomic nervous system dysfunction is well known to clinicians caring for patients with clinically manifest autonomic neuropathy. What is less appreciated is that even minor degrees of glucose intolerance are associated with abnormalities of autonomic balance. For example, among patients enrolled in a population-based cohort, the likelihood of an abnormal heart rate recovery increased in a steady fashion as fasting plasma glucose increased from 70 to 80 to 90 mg/dL and above **(Figure 5)**.[28] Even at levels of plasma glucose that would be considered normal, the likelihood of an abnormal heart rate recovery increased as plasma glucose increased.[28]

Perturbations of autonomic nervous system function have also been associated with environmental exposures. People who have lower levels of education,[29] live in neighborhoods characterized by lower socio-

economic status,[30] or are exposed to small-particulate air pollution[31] have been shown to manifest abnormal heart rate recovery or decreased heart rate variability.

CONCLUSIONS

Autonomic nervous system function can be measured in the clinic by recording resting heart rate, heart rate variability, or exercise heart rate recovery.[1] All three of these measures are strong predictors of cardiovascular risk and all-cause mortality in both primary and secondary prevention settings. A number of determinants of autonomic nervous system function have been identified, including patient-level factors like obesity, diabetes, and heart failure as well as environmental correlates like smoking, social stress, and air pollution. It is not yet known, however, how best to take advantage of the associations between abnormal autonomic nervous system function and poor prognosis to improve patient outcomes. Future research will be needed to identify strategies of favorably modulating autonomic function that improve outcomes in the clinic and among large populations.

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