Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 51, No. 18, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.01.038

STATE-OF-THE-ART PAPER

Assessment of Autonomic Function in Cardiovascular Disease

Physiological Basis and Prognostic Implications

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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.

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Manuscript received October 10, 2007; revised manuscript received December 20, 2007, accepted January 6, 2008.

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