ROBERT W. SHIELDS, JR, MD
Neuromuscular Center, Neurological Institute,
Cleveland Clinic, Cleveland, OH

Heart rate variability with deep breathing as a clinical test of cardiovagal function

ABSTRACT

Research into heart rate variability (HRV) and respiration over the past 150 years has led to the insight that HRV with deep breathing (HRVdb) is a highly sensitive measure of cardiovagal or parasympathetic cardiac function. This sensitivity makes HRVdb an important part of the battery of cardiovascular autonomic function tests used in clinical autonomic laboratories. HRVdb is a reliable and sensitive clinical test for early detection of cardiovagal dysfunction in a wide range of autonomic disorders.

Heart rate variability (HRV) has been a focus of interest in cardiovascular physiology for more than 150 years. This review will briefly survey the history of research linking HRV to respiration and then explore the clinical significance of this linkage, with a focus on HRV with deep breathing.

HRV AND RESPIRATION: THE EARLY RESEARCH

The first report linking HRV to respiration has been credited to Karl Ludwig, who in 1847 noted that heart rate increased with inspiration and decreased with expiration.[1,2] The precise origin of this variability has been studied extensively, but a single unifying mechanism defining the determinants of HRV with respiration has not been established. However, several mechanisms have been identified that may be contributing to HRV. Hering in 1871 noted in dog experiments that inflation of the lungs was associated with a tachycardia and that additional higher-pressure insufflation resulted in a bradycardia. He concluded that HRV was determined by pulmonary reflexes.[2,3] Bainbridge observed in dog experiments in 1915 that the heart rate increased during the diastolic filling of the heart that occurred during inspiration.[4] In a subsequent article, published in 1920, Bainbridge attributed HRV to this reflex, which now carries his name.[5]

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There is also evidence that HRV may be caused by central nervous system mechanisms. Canine experiments have revealed that rhythmic variations in the heart rate and ventricular pressure waves may coincide with rib cage movements in innervated, isovolumetric, left ventricular preparations.[6] These data are consistent with radiation of respiratory center activity to the cardiovascular autonomic centers in the medulla resulting in HRV. There is also evidence that stretch of the right atrium and sinus node region may produce HRV via cardiac reflexes.[7] It is likely that all of these mechanisms are contributing at some level to the HRV that is observed with respiration.

INSIGHTS INTO CLINICAL IMPLICATIONS

Clinical interest in HRV was sparked by the 1973 report of Wheeler and Watkins, who first drew attention to cardiac vagal innervation as the mediator of HRV and its potential value as a clinical test of cardiovagal function.[8] These investigators studied HRV with deep breathing (HRVdb) in normal subjects and diabetic subjects, some with and some without evidence of autonomic neuropathy. They noted that HRVdb was abolished by atropine, implying that the efferent component of the reflex is vagally mediated **(Figure 1)**. They also noted that HRVdb was reduced or abolished in diabetic subjects with autonomic neuropathy. They concluded that HRVdb was a clinically useful test for autonomic neuropathy in diabetic patients.

The relationship between vagal tone of the heart and HRV was further explored by Katona and Jih, who in 1975 reported on their experiments in a canine model.[9] They found a linear relationship between HRV as assessed by variations in heart period and parasympathetic control of the heart, defined as the difference in the average heart rate before and after complete abolishment of vagal innervation **(Figure 2)**. They concluded that the magnitude of the respiratory HRV is a measure of parasympathetic cardiac control. Fouad and colleagues duplicated this experiment in humans and found a similar linear relation-

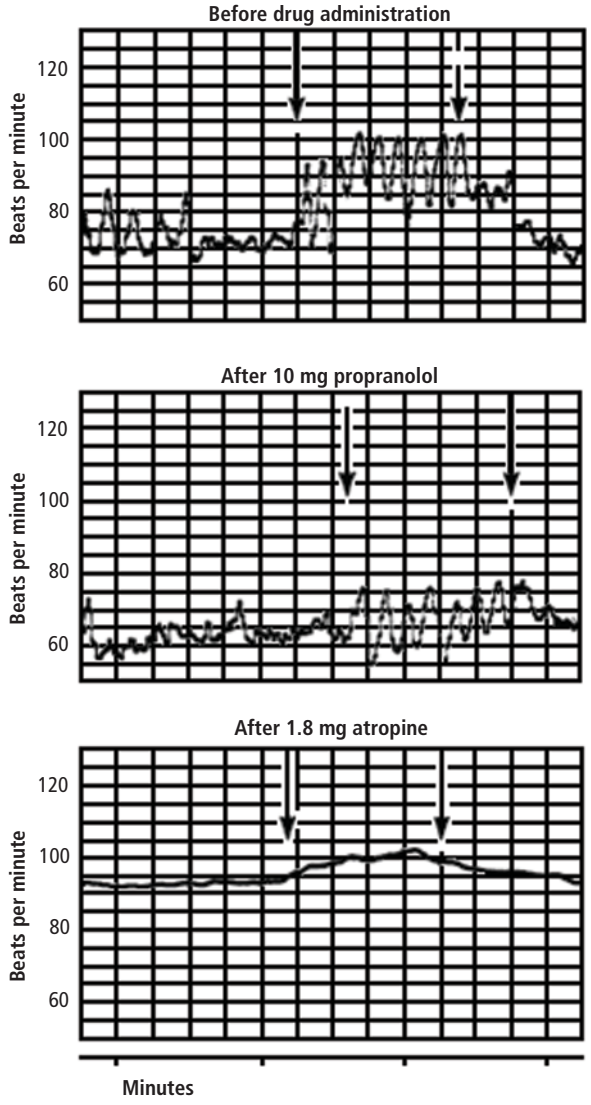

FIGURE 1. Heart rate variability with deep breathing in a healthy 30-year-old man under normal conditions (top panel) and after administration of intravenous propranolol (middle panel) and atropine (bottom panel).[8] Note how atropine abolishes the heart rate variability. Arrows indicate periods of deep breathing.

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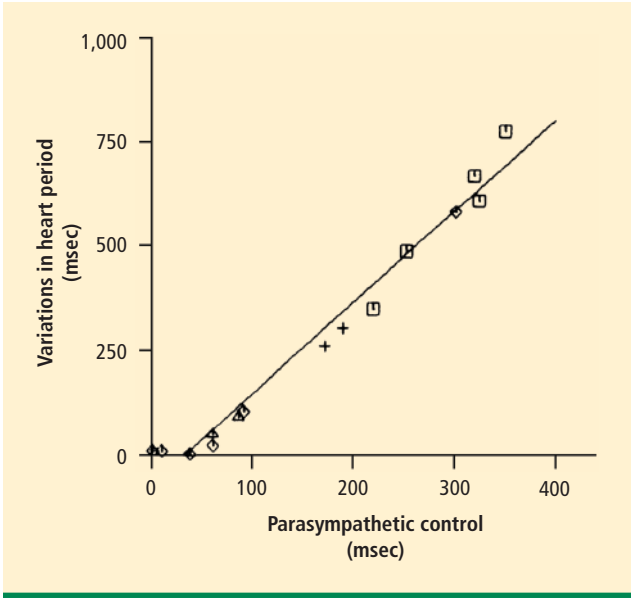

FIGURE 2. There is a linear relationship (correlation coefficient = 0.986) between respiratory variations in heart period and parasympathetic control, defined as the difference in the heart period before and after parasympathetic block. Data are from a series of experimental states in the canine: control (cross), propranolol block (triangle), propranolol block with phenylephrine HCl (square), and atropine (diamond).[9]

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ship between HRVdb and parasympathetic cardiac control, leading them to conclude that HRVdb is an accurate index of cardiac vagal tone **(Figure 3)**.[10]

METHODS OF MEASURING HRV

A wide variety of methods have been developed to measure HRV.[11,12] Some of the methods employ statistical analysis, typically of prolonged recordings of 24 hours or longer. These methods include simple statistics such as the standard deviation of the heart rate or the R-R interval as well as more complex statistical measures such as the mean squared successive difference of the R-R intervals. These methods have been applied mostly to the analysis of prognosis following acute myocardial infarction. Reduced HRV has been established as a powerful predictor of mortality and arrhythmic complications following acute myocardial infarction.[11] The methods developed for clinical tests of cardiovagal function typically involve measuring HRVdb over short intervals (< 90 sec). Deep breathing magnifies HRV with respiration, allowing for methods to assess HRV with respiratory cycles.

The two most widely used methods are the mean heart rate range (MHRR) and the expiratory-to-inspiratory ratio (E:I). The MHRR method is typically measured from a series of successive deep breaths, usually at least 6 breaths at a rate of 5 or 6 breaths per minute. The MHRR is calculated by subtracting the maximum heart rate during inspiration from the minimum heart rate during expiration for each cycle of breathing, and then determining the mean of these differences **(Figure 4)**.[12] The MHRR can also be measured from a single breath.[13] The E:I ratio assesses the ratio of the longest R-R interval during expiration to the shortest R-R interval during inspiration.[12] The E:I ratio may also be assessed from a

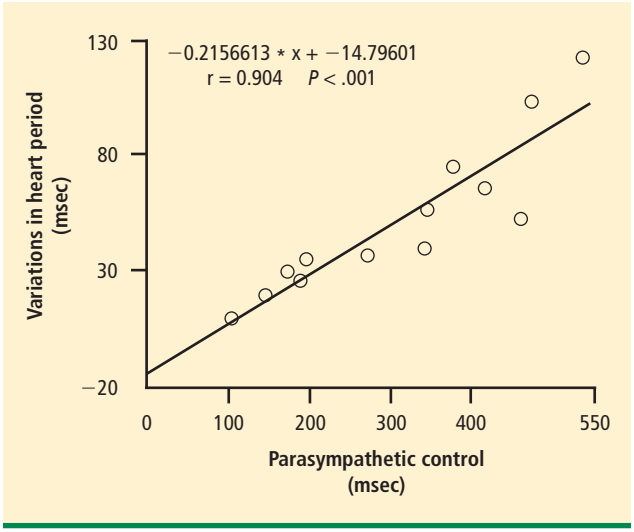

FIGURE 3. Consistent with the animal findings in Figure 2, there is a linear relationship between variations in heart period and parasympathetic control (defined as the difference in the heart period before and after atropine block) in humans as well, as demonstrated by Fouad et al.[10]

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single breath or the mean of successive breaths.[14]

Analysis of HRV has also been studied in the frequency domain by using Fourier transformation and converting heart rate to a power spectrum.[15,16] The peak power at the highest frequencies (> 0.15 Hz) reflects respiratory sinus arrhythmia, while the lower frequencies reflect both sympathetic and parasympathetic influences. In a comparison of low-frequency power, high-frequency power, and total power to standard methods of measuring HRVdb, all of these spectral measures were proven to be strong predictors of the results from the standard methods.[16] Marked reduction in the power spectrum was noted in patients with diabetic autonomic neuropathy **(Figure 5)**.[16]

FACTORS THAT AFFECT HRV WITH DEEP BREATHING

Many variables may affect HRVdb.[12] HRVdb is influenced by age, as the variability decreases with advancing age, so it is essential to use methods with well-defined age-stratified normal values. HRVdb is maximal when the patient is lying supine and breathing at a rate of 5 to 6 breaths per minute. The depth of breathing for a maximum result requires a tidal volume of approximately 1.2 L for an average adult. Protocols that involve breathing for more than 90 seconds may induce hypocapnea, which can reduce HRVdb. Most importantly, numerous medications can affect HRVdb. Medications with anticholinergic activity, including over-the-counter cold medications, tricylic antidepressants, and antispasmodics, should be discontinued at least 48 hours prior to testing, if possible. Patients are also instructed to not drink caffeinated beverages, use nicotine, or drink alcohol 3 hours prior to testing.

CLINICAL APPLICATIONS

HRVdb represents a very sensitive measure of cardiovagal or parasympathetic cardiac function and thus is an important component of the battery of cardiovascular autonomic function tests used in clinical autonomic laboratories. In most autonomic disorders, parasympathetic function is affected before sympathetic function, so HRVdb provides a sensitive screening measure for parasympathetic dysfunction in many autonomic disorders. HRVdb has proven to be a sensitive and reliable clinical test for the early detection of cardiovagal dysfunction in a wide spectrum of autonomic disorders, including diabetic autonomic neuropathy,[14] uremic neuropathy,[17] familial autonomic neuropathies,[18] and various small fiber neuropathies.[19,20] HRVdb has also been valuable in assessing patients with pure autonomic failure,[21] multisystem atrophy,[22] and other central neurodegenerative disorders.[23]

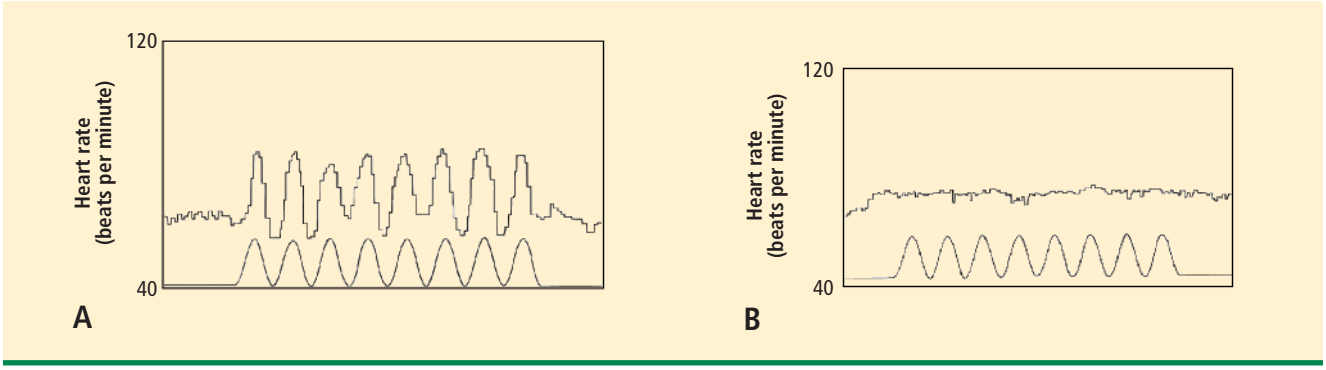

FIGURE 4. Heart rate response to deep breathing in **(A)** a normal control and **(B)** a patient with autonomic neuropathy. (Respiratory pattern is illustrated as a sine wave of 6 cycles per minute.) Note how heart rate variability is severely depressed in the patient with autonomic neuropathy.

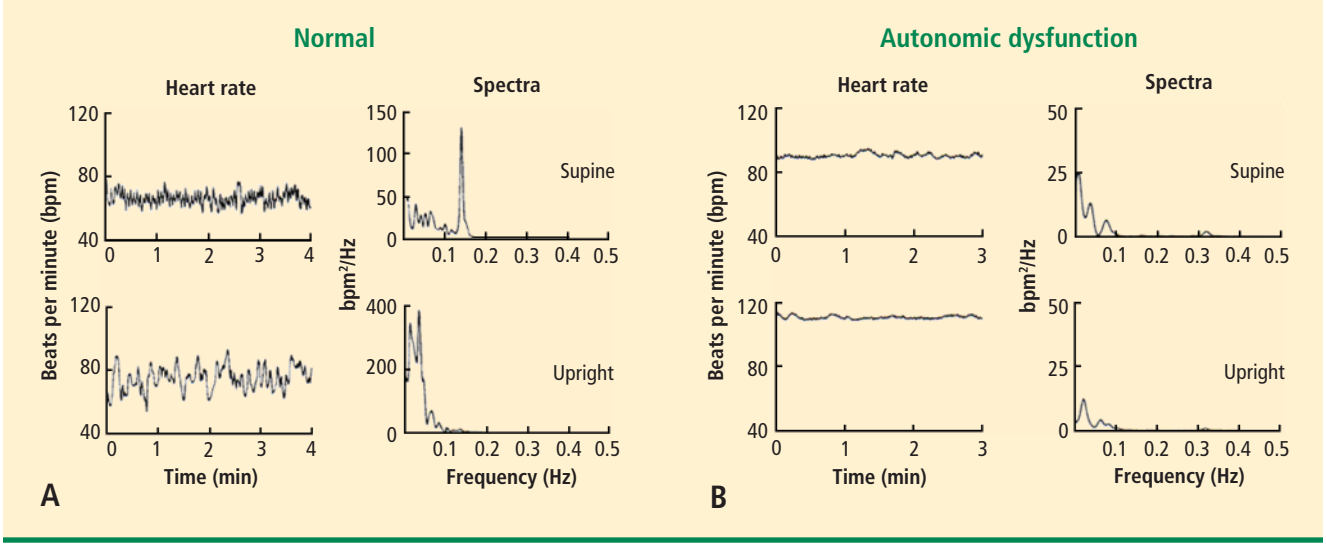

FIGURE 5. Power spectrum of **(A)** the normal resting heart rate and **(B)** the resting heart rate of a diabetic patient with severe autonomic dysfunction.[16] Note the severe loss of power at all frequencies for the patient with severe autonomic dysfunction (note the lower y-axis scale of the power spectrum for this patient).

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Correspondence: *Robert W. Shields, Jr, MD, Neuromuscular Center, Cleveland Clinic, 9500 Euclid Avenue, S90, Cleveland, OH 44195; shieldr@ccf.org*