

| REPORT DOCUMENTATION PAGE  |  |  | Form Approved<br>OMB No. 0704-0188 |
|--|--|--|------------------------------------|
| Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503. |  |  |                                    |
| 1. AGENCY USE ONLY (Leave blank)   | 2. REPORT DATE<br>15.Jul.04              | 3. REPORT TYPE AND DATES COVERED<br>MAJOR REPORT         |                                    |
| 4. TITLE AND SUBTITLE<br>HEART RATE VARIABILITY ANALYSIS IN THE ASSESSMENT OF AUTONOMIC FUNCTION IN HEART FAILURE  |  | 5. FUNDING NUMBERS                                       |                                    |
| 6. AUTHOR(S)<br>MAJ DEJONG MARLA J   |  |  |                                    |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br>UNIVERSITY OF KENTUCKY LEXINGTON   |  | 8. PERFORMING ORGANIZATION REPORT NUMBER<br><br>CI04-465 |                                    |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)<br>THE DEPARTMENT OF THE AIR FORCE<br>AFIT/CIA, BLDG 125<br>2950 P STREET<br>WPAFB OH 45433  |  | 10. SPONSORING/MONITORING AGENCY REPORT NUMBER           |                                    |
| 11. SUPPLEMENTARY NOTES  |  |  |                                    |
| 12a. DISTRIBUTION AVAILABILITY STATEMENT<br>Unlimited distribution<br>In Accordance With AFI 35-205/AFIT Sup 1   |  | 12b. DISTRIBUTION CODE                                   |                                    |
| 13. ABSTRACT (Maximum 200 words)   |  |  |                                    |
| <p><b>DISTRIBUTION STATEMENT A</b><br/>Approved for Public Release<br/>Distribution Unlimited</p> <p><b>20040730 044</b></p>   |  |  |                                    |
| 14. SUBJECT TERMS  |  | 15. NUMBER OF PAGES<br>35                                |                                    |
|  |  | 16. PRICE CODE   |                                    |
| 17. SECURITY CLASSIFICATION OF REPORT  | 18. SECURITY CLASSIFICATION OF THIS PAGE | 19. SECURITY CLASSIFICATION OF ABSTRACT                  | 20. LIMITATION OF ABSTRACT         |

**Title:** Heart Rate Variability Analysis in the Assessment of Autonomic Function in Heart Failure

**Authors:**

- Marla J. De Jong, RN, MS, CCNS, CCRN, CEN, Major  
Doctoral Student  
University of Kentucky, College of Nursing / United States Air Force  
Lexington, KY
- David C. Randall, PhD  
Professor  
Department of Physiology  
University of Kentucky, College of Medicine  
Lexington, KY

**Contact Author:** Marla J. De Jong  
527 College of Nursing  
University of Kentucky  
Lexington, KY 40536  
Telephone: (859) 323-6687  
FAX: (859) 223-7265  
E-mail: mdejong@aol.com

**Institution Where the Work Was Performed:** University of Kentucky, College of Nursing and College of Medicine

**Disclaimer Statement:** The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force or the Department of Defense.

**Abstract**

Heart rate is not static but rather changes continuously in response to physical and mental demands. In fact, an invariant heart rate is associated with disease processes such as heart failure. Heart rate variability analysis is a noninvasive technique used to quantify fluctuations in heart rate. In this paper, we review neural control of heart rate, briefly describe heart rate variability, and summarize research data demonstrating that heart failure is associated with altered heart rate variability. In addition, we present evidence that heart failure patients with decreased heart rate variability are at risk for future cardiac events, need for heart transplantation, and death.

**Key Words:** Heart failure, heart rate variability, autonomic nervous system

Clinicians often report that a patient's heart rate (HR) is "regular." Yet, as shown in Figure 1, HR is not a static hemodynamic parameter, but rather changes over time in response to physical and mental demands. Furthermore, an invariant, or nearly invariant, HR is often associated with disease processes such as heart failure (HF),<sup>1-5</sup> acute myocardial infarction (AMI),<sup>6-10</sup> and diabetes.<sup>11</sup> Heart rate variability (HRV) analysis is a noninvasive technique used to quantify fluctuations in HR that reflect naturally occurring physiological processes.<sup>12</sup> The purpose of this paper is to review neural control of HR, briefly describe HRV, and summarize research findings about HRV for patients with HF.

### **Neural Control of Heart Rate**

Heart rate is normally determined by spontaneous and periodic depolarizations of the sino-atrial node. Although neural innervation is not necessary to initiate the heart beat, the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS), the intrinsic cardiac nervous system, reflexes, and respiration modulate the frequency of sino-atrial nodal depolarizations. These neural systems also influence cardiac contractility and conduction of electrical activity through the heart. Accordingly, cardiac chronotropism (HR), inotropism (contractility), and dromotropism (conduction, primarily through the AV node) are adjusted to meet the changing needs of the body.

### *Sympathetic Nervous System*

Sympathetic nervous system fibers emerge from the cell bodies of preganglionic neurons within the intermediolateral column of the spinal cord located in the thoracic through lumbar (T1-L2) regions. After passing through the white rami, most fibers synapse with postganglionic efferent neurons within the sympathetic paravertebral ganglia. The axons of these postganglionic neurons innervate blood vessels and the viscera.<sup>13</sup>

### *Parasympathetic Nervous System*

Parasympathetic nervous system fibers emerge from cell bodies of the preganglionic neurons located in the brainstem and sacral area (S2-S4). Parasympathetic nerves travel to the head, thorax, and abdomen within cranial nerves. The vagus nerve (i.e., cranial nerve X) provides the parasympathetic innervation to the heart, lungs, and some abdominal regions. The majority of the axons within this nerve are sensory (i.e., visceral afferent); only about 20% of these axons are motor (i.e., parasympathetic efferent).

Like sympathetic nerves, the vagus nerve innervates the sinus and atrioventricular nodes and the atrial myocardium. The classical view that there is little to no parasympathetic innervation of ventricular myocardium neglects the well-established fact that parasympathetic nerves presynaptically inhibit the release of neurotransmitter from sympathetic nerves innervating ventricular myocardium; this “indirect” effect can profoundly affect ventricular contractile function.<sup>13-15</sup> Vagal stimulation promotes acetylcholine release which decreases HR, myocardial conduction, atrial contractility, and through interaction with the sympathetic system, ventricular contractility.<sup>13,14</sup>

### *Functional Connectivity Between the Sympathetic and Parasympathetic Systems*

The heart and the majority of other organs are innervated by both sympathetic and parasympathetic nerves (i.e., reciprocal innervation). In resting man, parasympathetic effects predominate sympathetic effects on HR. Whereas activity in the cardiac parasympathetic efferent nerves produces changes in HR on a beat to beat basis,<sup>16</sup> typically, many seconds elapse before changes in cardiac sympathetic nervous activity achieve peak effects. Thus, as is explained below, these short latency effects of vagal activation ultimately explain the dominance of the parasympathetic nervous system within the “high frequency” range of the HR power

spectrum. Conversely, alterations in sympathetic activity produce large amplitude, but slowly developing, or “low frequency” changes in HR. In general, sympathetic stimulation is associated with diminished parasympathetic activity; the opposite is also true.<sup>17</sup>

### *Intrinsic Cardiac Nervous System*

Recently, the anatomy of function of a nervous network within the heart itself has been extensively studied. Intrinsic cardiac ganglia have been described in five regions on the posterior surface of the atria and in five regions on the superior aspect of the ventricles.<sup>18</sup> The ICN reportedly includes not only the classically described parasympathetic post-ganglionic neurons, but also sensory neurons, interneurons and catecholaminergic (i.e., “sympathetic”) neurons. The “intrinsic cardiac network” (ICN) formed by these elements is effectually a localized component of the ANS analogous to the enteric nervous system in the gut. The cardiac ICN appears to be capable of mediating intracardiac reflexes.<sup>14</sup> Canines with early-stage HF manifested altered intrinsic cardiac nervous function and a compromised ability to regulate HR and other hemodynamic variables.<sup>19</sup> Thus, neural control of HR is likely a function of both the intrinsic cardiac and autonomic nervous systems.<sup>15</sup>

### *Autonomic Neuropharmacology*

Norepinephrine is released from the sympathetic nerve varicosities; it interacts with  $\beta$  adrenergic receptors in the heart to produce positive chronotropic, dromotropic or inotropic effects, depending upon the tissue under consideration. Newer evidence has shown that the heart itself synthesizes norepinephrine.<sup>20,21</sup> Parasympathetic post-ganglionic fibers release acetylcholine that then interacts with muscarinic cholinergic receptors. Activation of these receptors, again depending upon the specific tissue, produces negative chronotropic, dromotropic and, in the atria, inotropic effects. Although their function has not been fully elucidated, it is

known that numerous putative neurotransmitters are co-released with these “classical” neurotransmitters. These include, for example, adenosine 5'-triphosphate, adenosine, 5-hydroxytryptamine, neuropeptide Y, vasoactive intestinal polypeptide, somatostatin, nitric oxide, carbon monoxide, and histamine.<sup>22</sup>

### *Reflex Control of Cardiovascular Function*

Receptors within the aortic arch and carotid sinus sense blood pressure changes and modify HR to maintain hemodynamic stability. For example, if blood pressure increases, the baroreceptors fire more rapidly and transmit impulses to the nucleus tractus solitarius (NTS) in the brainstem.<sup>23</sup> Neurons from the NTS project to the nucleus ambiguus and stimulate parasympathetic preganglionic neurons which, in turn, project through the vagus nerve to parasympathetic ganglia at the heart.<sup>23</sup> At the same time, activity within the sympathetic nerves is decreased. As a result, HR, peripheral vascular resistance, and cardiac output decrease and blood pressure normalizes.

Increased right atrial pressure distends atrial mechanoreceptors which transmit impulses to the brainstem via vagal afferent nerves. Unlike the baroreflex, this Bainbridge reflex is a “feed forward” mechanism whereby efferent sympathetic stimulation produces tachycardia and thus enables the heart to effectively pump the larger preload. However, the magnitude and direction of the HR response depend on the baseline HR and concomitant baroreceptor reflex activity.<sup>13</sup>

### *Respiratory Sinus Arrhythmia*

Respiratory sinus arrhythmia (RSA) refers to the cyclical variation in HR interval associated with respiration and is primarily attributable to oscillations in efferent activity in the vagal fibers innervating the sino-atrial node (Figure 2).<sup>24</sup> During inspiration, lung distention

stimulates vagal afferent nerves in the lungs. In the brainstem, these vagal sensory impulses ultimately inhibit vagal efferent activity, thereby increasing HR. With expiration, HR decreases secondary to increased cardiac vagal activity. This is one mechanism whereby breathing has a profound impact on HR fluctuations.<sup>25</sup> Other data suggest that sympathetic activity also influences RSA at both slow and rapid breathing rates.<sup>26</sup> Respiratory sinus arrhythmia may improve the efficiency of pulmonary gas exchange.<sup>27</sup>

### **Heart Rate Variability**

The RR interval on the electrocardiogram (ECG) is the time between two ventricular beats and thus can be used to calculate ventricular rate. For example, the RR interval is 0.8 sec when HR is 75 beats/min. Heart rate variability refers to the increases and decreases over time in the RR interval.<sup>28,29</sup> Very slowly occurring changes in the RR interval have been attributed to alterations in vasomotor tone associated with thermoregulation.<sup>30,31</sup> More rapid changes in the RR interval are produced by the baroreceptor reflex.<sup>24</sup> As has already been explained, rather rapid changes in RR interval are produced by respiration. Normal aging is associated with decreased HRV.<sup>32</sup> Much of the current interest in HRV stems from reports that “power” within select frequency ranges provides evidence regarding the ANS and its effectors. Although HRV analysis does not directly measure autonomic nervous activity,<sup>33</sup> HRV data have prognostic value for patients with HF.<sup>1,4,34-36</sup>

The first step of HRV analysis is to acquire a quality ECG recording; for typical applications, an artifact-free recording of five minutes' duration is generally adequate, although longer data sets are required in more specialized circumstances.<sup>37</sup> Using a computer and commercial software, the ECG analog signal is then converted to a digital signal. The computer also generates the RR tachogram which is a series of time intervals between two consecutive R

waves. Time-domain and frequency-domain analyses are the approaches most often used to quantify HRV. Nonlinear methods such as Poincaré plots have also been used to study patients with HF,<sup>38,39</sup> though this methodology will not be considered here.

#### *Time-Domain Analyses*

Time-domain analyses are statistical calculations of RR intervals (also termed normal-to-normal [NN] intervals) and are relatively easy to compute. Using the RR tachogram, computer software calculates the sequential NN intervals of adjacent R waves produced by a sinus pacemaker; any ventricular ectopic beats are edited from the record. The software also computes the differences between NN intervals. Other time-domain measures that can then be derived include: 1) standard deviation of all NN intervals for a selected time period (SDNN), 2) standard deviation of the mean of NN intervals in all 5-minute segments of the recording period (SDANN), 3) square root of the mean squared differences of successive NN intervals (RMSSD), 4) the number of pairs of successive NN intervals differing by greater than 50 ms in the recording period (NN50 count), and 5) the proportion of differences in successive NN intervals greater than 50 ms (pNN50).<sup>28</sup> Although most investigators calculate pNN50 values, in one study NN12 values best differentiated between healthy persons and patients with HF.<sup>2</sup> In the same study, patients with New York Heart Association (NYHA) class I-II HF had higher pNN10, but not pNN50, values than patients with class III-IV HF. Numerically smaller time-domain values denote lower HRV.

#### *Frequency-Domain Analysis*

For frequency-domain (or spectral) analysis of the RR tachogram, computer software uses an mathematical algorithm, such as fast Fourier transformation, to apportion the HRV signal into its frequency components (Figure 3) and to quantify the power of these components. To

understand this process more clearly, consider that any “signal” contains information that ranges from components that change very slowly (i.e., low frequency) to components that fluctuate rapidly. The relative admixture of the various frequency components is often of considerable importance. For example, the overall sound generated by a mixed choir of male and female voices includes the very low frequencies of the base section, the somewhat higher frequencies of the tenors, as well as the much higher frequencies produced by the alto and soprano singers. The conductor, in analyzing the quality of the performance, can mentally perform a “frequency domain analysis” to discern the individual notes produced by each section (e.g., are the tenors “in tune?”), and assess the intensity of each part (e.g., is the mixture of the volume of sound from the bases and sopranos appropriately balanced?). Likewise, spectral, or frequency-domain analysis, precisely quantifies the power of fluctuations in HR over a designated range of frequencies.<sup>40</sup> Unlike time-domain measures, frequency-domain measures can quantitate rhythms and their frequencies.<sup>25</sup>

Frequency-domain results are displayed by plotting the magnitude of HRV power against frequency. Three frequency bands are of clinical interest: 1) very-low frequency (VLF) band (0.003-0.04 Hz), 2) low frequency (LF) band (0.04-0.15 Hz), and 3) high frequency band (0.15-0.4 Hz).<sup>28</sup> In humans, VLF, LF and high frequency peak frequencies are commonly centered around about 0.015 Hz, 0.1 Hz and 0.25 Hz, respectively. In some contexts an ultra-low frequency band (ULF;  $\leq 0.003$  Hz) is also of interest.<sup>41,42</sup> Figure 3 is an illustrative heart rate power spectrum computed by a mathematical process known as “Fast Fourier Transform<sup>1</sup>”; it

---

<sup>1</sup> The computations involved in the Fast Fourier Transform, or FFT, have been included in most of the commercial software that is now widely available for HRV analysis. It is important to bear in mind, however, that there are a number of important requirements for valid computations. For example, any signal subject to FFT must be “stationary,” meaning that the statistical characteristics of the signal (e.g., mean value, variance) are the same throughout the course of the recording. The algorithm assumes these conditions have been met, when, in fact, one or more may be violated by a given data set. One must assure him/herself that these requirements are satisfied before performing the computation if valid results are to be obtained.

shows concentrations of power within the three major bands. The area under the curve of each frequency band represents the power within that band. Normally, LF power exceeds high frequency power. Total power represents the variability of the entire signal and is obtained by summing the powers of each frequency band. Low frequency and high frequency power are often “normalized” (i.e., expressed as a percentage of total power), by dividing each by the total power minus VLF power,<sup>43</sup> although in Figure 3 power is given in absolute units of beats-per-minute squared.

Although some have cautioned that respiration itself may be responsible for observed changes in HRV,<sup>24,44,45</sup> it is generally believed that specific physiological processes contribute differently to power within the various regions. For example, it is commonly accepted that respiratory mechanisms mediate high frequency components of HRV.<sup>12,27,46-48</sup> Recall that HR responds very quickly to changes in the nervous activity in the parasympathetic nerves innervating the sino-atrial node. This rapid response characteristic ultimately assures that the HF peak of the HR power spectrum is mediated largely, probably exclusively, by the parasympathetic nervous system.<sup>46</sup> Conversely, the sympathetic system is unable to mediate high frequency components because the sino-atrial nodal response to changes in norepinephrine interacting with the  $\beta$ -adrenergic receptor is much slower than that of acetylcholine interacting with the muscarinic receptors.<sup>40,49</sup> Thus, the high frequency component provides data about how the sino-atrial node responds to vagal activity at the respiratory frequency.

In contrast, a mixture of sympathetic and parasympathetic activities is generally thought to influence the LF components of HRV.<sup>12,46,47</sup> As such, the LF component provides information about autonomic tone; however, evidence suggests that parasympathetic activity dominates at

higher frequencies.<sup>50</sup> The circadian rhythm accounts for much of the variation in the ultra-low frequency band.<sup>51</sup>

Some<sup>17,28,49</sup> investigators argue that the ratio of power within the low frequency vs. high frequency spectral regions (i.e., low frequency:high frequency ratio) distinguishes sympathetic effects from parasympathetic effects. However, this is controversial<sup>48,52</sup> and caution is warranted in drawing any conclusions in this regard. Although the sympathetic and parasympathetic systems function on a reciprocal basis, these systems are not necessarily “balanced.”<sup>48</sup>

### **Heart Rate Variability and Heart Failure**

It is well known that a hallmark of HF is adverse changes in autonomic function that are manifested, in part, by altered HRV. Heart failure ensues following myocardial cell damage that impairs ventricular contractility. Neurohormonal systems are activated in an attempt to maintain cardiac output and tissue perfusion.<sup>53</sup> Nonetheless, chronic neurohormonal activation ultimately contributes to progressively deteriorating HF.<sup>53</sup> Fundamentally, HF is characterized by profoundly elevated sympathetic activity for an extended period. Although perhaps less well documented, parasympathetic withdrawal is also an important facet of HF.<sup>47,54</sup>

Heart rate variability analysis enables clinicians and researchers to detect, quantify, and trend changes in autonomic activity for patients with HF. However, spectral analysis is difficult for patients with terminal HF because HR is often nearly invariant.<sup>47</sup>

As shown in Table 1, patients with HF exhibit altered HRV in both the time and frequency domains. High sympathetic activity,<sup>55-57</sup> neuroendocrine dysfunction,<sup>40</sup> elevated cytokine levels,<sup>58</sup> and reduced vagal-cardiac activity<sup>52</sup> contribute to decreased HRV for patients with HF. Patients with decreased HRV have difficulty employing vagal mechanisms to counteract sympathetic activation.<sup>59</sup> Others<sup>60,61</sup> have reported that patients with HF have

decreased LF power which seemingly contradicts the thought that HF is associated with high sympathetic tone. It is possible, therefore, that HRV analysis may be difficult to interpret for groups of individuals, for example, patients with HF compared with healthy persons.

Importantly, decreased HRV is associated with adverse outcomes as shown in Table 2. In summary, time-domain HRV parameters predict mortality<sup>1,4,36,62-65</sup> and future cardiac events.<sup>34</sup> In addition, frequency-domain parameters reportedly predict mortality,<sup>1,35,64,66</sup> sudden death,<sup>5,62</sup> and need for heart transplantation.<sup>67</sup>

Although HRV data are useful, they cannot be interpreted reliably without attention to comorbid conditions,<sup>49</sup> medication therapy,<sup>21</sup> body position,<sup>68</sup> emotions,<sup>69,70</sup> circadian rhythm,<sup>32</sup> and other variables known to affect the ANS. For example, patients with HF had higher high frequency power, lower LF power, and lower HF:LF ratio values in the right lateral decubitus position than in supine or left lateral positions.<sup>68</sup> Moreover, beta-blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists may exert their morbidity and mortality benefits by minimizing ANS and neurohormonal disturbances.<sup>21</sup>

In summary, the sympathetic and parasympathetic nervous systems, reflexes, and respiration influence HR. Heart rate variability analysis enables clinicians and researchers to examine the influences of autonomic activity on HR. A consistent finding for patients with HF is decreased

HRV. Importantly, this decreased HRV is associated with adverse outcomes.

## References

1. Makikallio TH, Huikuri HV, Hintze U, et al. Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure. *Am J Cardiol.* 2001;87:178-182.
2. Mietus JE, Peng C-K, Henry I, Goldsmith RL, Goldberger AL. The pNNx files: re-examining a widely used heart rate variability measure. *Heart.* 2002;88:378-380.
3. Malave HA, Taylor AA, Nattama J, Deswal A, Mann DL. Circulating levels of tumor necrosis factor correlate with indexes of depressed heart rate variability: a study in patients with mild-to-moderate heart failure. *Chest.* 2003;123:716-724.
4. Bilchick KC, Fetics B, Djoukeng R, et al. Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). *Am J Cardiol.* 2002;90:24-28.
5. La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation.* 2003;107:565-570.
6. Tapanainen JM, Thomsen PE, Kober L, et al. Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. *Am J Cardiol.* 2002;90:347-352.
7. Bigger JT, Jr., Steinman RC, Rolnitzky LM, Fleiss JL, Albrecht P, Cohen RJ. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. *Circulation.* 1996;93:2142-2151.

8. Bigger JT, Jr., Fleiss JL, Steinman RC, Rolnitzky LM, Schneider WJ, Stein PK. RR variability in healthy, middle-aged persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. *Circulation*. 1995;91:1936-1943.
9. Bigger JT, Jr., Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation*. 1993;88:927-934.
10. Katz A, Liberty IF, Porath A, Ovsyshcher I, Prystowsky EN. A simple bedside test of 1-minute heart rate variability during deep breathing as a prognostic index after myocardial infarction. *Am Heart J*. 1999;138:32-38.
11. Migliaro ER, Canetti R, Contreras P, Hakas M. Heart rate variability: short-term studies are as useful as holter to differentiate diabetic patients from healthy subjects. *Annals of Noninvasive Electrocardiology*. 2003;8:313-320.
12. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science*. 1981;213:220-222.
13. Berne RM, Levy MN. Principles of physiology. St. Louis: Mosby, 2000.
14. Randall DC, Brown DR, McGuirt AS, Thompson GW, Armour JA, Ardell JL. Interactions within the intrinsic cardiac nervous system contribute to chronotropic regulation. *Am J Physiol Regul Integr Comp Physiol*. 2003;285:R1066-1075.
15. Armour JA, Ardell JL. Basic and Clinical Neurocardiology. New York: Oxford University Press, 2004.
16. Greenwood JP, Batin PD, Nolan J. Assessment of cardiac autonomic function. *Br J Cardiol*. 1997;3:154-157.

17. Malliani A. The pattern of sympathovagal balance explored in the frequency domain. *News Physiol Sci.* 1999;14:111-117.
18. Armour JA, Murphy DA, Yuan B-X, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec.* 1997;247:289-298.
19. Arora RC, Cardinal R, Smith FM, Ardell JL, Dell'Italia LJ, Armour JA. Intrinsic cardiac nervous system in tachycardia induced heart failure. *Am J Physiol Regul Integr Comp Physiol.* 2003;285:R1212-1223.
20. Mann DL. Mechanisms and models in heart failure: a combinatorial approach. *Circulation.* 1999;100:999-1008.
21. Mann DL, Deswal A, Bozkurt B, Torre-Amione G. New therapeutics for chronic heart failure. *Annu Rev Med.* 2002;53:59-74.
22. Crick SJ, Sheppard MN, Anderson RH. Neural supply of the heart. In: Ter Horst GJ, ed. *The nervous system and the heart.* Totowa, New Jersey: Humana Press, 2000:3-54.
23. Richardson DR, Randall DC, Speck DF. *Quick look: cardiopulmonary system.* Madison, CN: Fence Creek Publishing, 1999.
24. Malpas SC. Neural influences on cardiovascular variability: possibilities and pitfalls. *Am J Physiol Heart Circ Physiol.* 2002;282:H6-20.
25. Eckberg DL. The human respiratory gate. *J Physiol (Lond).* 2003;548:339-352.
26. Taylor JA, Myers CW, Halliwill JR, Seidel H, Eckberg DL. Sympathetic restraint of respiratory sinus arrhythmia: implications for vagal-cardiac tone assessment in humans. *Am J Physiol Heart Circ Physiol.* 2001;280:H2804-2814.
27. Yasuma F, Hayano J. Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm? *Chest.* 2004;125:683-690.

28. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996;93:1043-1065.
29. Kara T, Nykodym J, Somers VK. Heart rate variability: back to the beginning. *J Cardiovasc Electrophysiol*. 2003;14:800-802.
30. Matsumoto T, Miyawaki T, Ue H, Kanda T, Zenji C, Moritani T. Autonomic responsiveness to acute cold exposure in obese and non-obese young women. *Int J Obes*. 1999;23:793-800.
31. Fleisher LA, Frank SM, Sessler DI, Cheng C, Matsukawa T, Vannier CA. Thermoregulation and heart rate variability. *Clin Sci*. 1996;90:97-103.
32. Bonnemeier H, Wiegand UK, Brandes A, et al. Circadian profile of cardiac autonomic nervous modulation in healthy subjects: differing effects of aging and gender on heart rate variability. *J Cardiovasc Electrophysiol*. 2003;14:791-799.
33. Esler M, Kaye D, Lambert G, Esler D, Jennings G. Adrenergic nervous system in heart failure. *Am J Cardiol*. 1997;80:7L-14L.
34. Fauchier L, Babuty D, Cosnay P, Autret ML, Fauchier JP. Heart rate variability in idiopathic dilated cardiomyopathy: characteristics and prognostic value. *J Am Coll Cardiol*. 1997;30:1009-1014.
35. Ponikowski P, Anker SD, Chua TP, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1997;79:1645-1650.

36. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation*. 1998;98:1510-1516.
37. Brown DR, Randall DC, Knapp CF, Lee KC, Yingling JD. Stability of the heart rate power spectrum over time in the conscious dog. *FASEB J*. 1989;3:1644-1650.
38. Woo MA, Stevenson WG, Moser DK, Trelease RB, Harper RM. Patterns of beat-to-beat heart rate variability in advanced heart failure. *Am Heart J*. 1992;123:704-710.
39. Woo MA, Stevenson WG, Moser DK, Middlekauff HR. Complex heart rate variability and serum norepinephrine levels in patients with advanced heart failure. *J Am Coll Cardiol*. 1994;23:565-569.
40. Pumpura J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: physiological basis and practical applications. *Int J Cardiol*. 2002;84:1-14.
41. Burgess DE, Zimmerman TA, Wise MT, Li S-G, Randall DC, Brown DR. Low-frequency renal sympathetic nerve activity, arterial BP, stationary "1/f noise," and the baroreflex. *Am J Physiol*. 1999;277:R894-903.
42. Burgess DE, Randall DC, Speakman RO, Brown DR. Coupling of sympathetic nerve traffic and BP at very low frequencies is mediated by large-amplitude events. *Am J Physiol Regul Integr Comp Physiol*. 2003;284:R802-810.
43. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation*. 1991;84:482-492.

44. Bernardi L, Wdowczyk-Szulc J, Valenti C, et al. Effects of controlled breathing, mental activity and mental stress with or without verbalization on heart rate variability. *J Am Coll Cardiol.* 2000;35:1462-1469.
45. Pinna GD, Maestri R, Rovere MT, Mortara A. An oscillation of the respiratory control system accounts for most of the heart period variability of chronic heart failure patients. *Clin Sci.* 1996;91:89-91.
46. Randall DC, Brown DR, Raisch RM, Yingling JD, Randall WC. SA nodal parasympathectomy delineates autonomic control of heart rate power spectrum. *Am J Physiol.* 1991;260:H985-988.
47. Floras JS. Alterations in the sympathetic and parasympathetic nervous system in heart failure. In: Mann DL, ed. Heart failure: a companion to Braunwald's heart disease. Philadelphia: Saunders, 2004:247-277.
48. Eckberg DL. Sympathovagal balance: a critical appraisal. *Circulation.* 1997;96:3224-3232.
49. Greenwood JP, Durham NP, Nolan J. Autonomic assessment of cardiovascular disease. *Hosp Med.* 1998;59:714-718.
50. Taylor JA, Carr DL, Myers CW, Eckberg DL. Mechanisms underlying very-low-frequency RR-interval oscillations in humans. *Circulation.* 1998;98:547-555.
51. Stauss HM. Heart rate variability. *Am J Physiol Regul Integr Comp Physiol.* 2003;285:R927-931.
52. Eckberg DL. Physiological basis for human autonomic rhythms. *Ann Med.* 2000;32:341-349.

53. Mann DL. Heart failure as a progressive disease. In: Mann DL, ed. Heart failure: a companion to Braunwald's heart disease. Philadelphia: Saunders, 2004:123-128.
54. Binkley PF, Nunziata E, Haas GJ, Nelson SD, Cody RJ. Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. *J Am Coll Cardiol.* 1991;18:464-472.
55. Tygesen H, Rundqvist B, Waagstein F, Wennerblom B. Heart rate variability measurement correlates with cardiac norepinephrine spillover in congestive heart failure. *Am J Cardiol.* 2001;87:1308-1311.
56. Yoshikawa T, Baba A, Akaishi M, et al. for the Keio Interhospital Cardiology Study (KICS) Investigators. Neurohumoral activations in congestive heart failure: correlations with cardiac function, heart rate variability, and baroreceptor sensitivity. *Am Heart J.* 1999;137:666-671.
57. Burger AJ, Aronson D. Activity of the neurohormonal system and its relationship to autonomic abnormalities in decompensated heart failure. *J Card Fail.* 2001;7:122-128.
58. Aronson D, Mittleman MA, Burger AJ. Interleukin-6 levels are inversely correlated with heart rate variability in patients with decompensated heart failure. *J Cardiovasc Electrophysiol.* 2001;12:294-300.
59. La Rovere MT, Bigger JT, Jr., Marcus FI, Mortara A, Schwartz PJ for the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet.* 1998;351:478-484.

60. van de Borne P, Montano N, Pagani M, Oren R, Somers VK. Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. *Circulation*. 1997;95:1449-1454.
61. Scalvini S, Volterrani M, Zanelli E, et al. Is heart rate variability a reliable method to assess autonomic modulation in left ventricular dysfunction and heart failure? Assessment of autonomic modulation with heart rate variability. *Int J Cardiol*. 1998;67:9-17.
62. Galinier M, Pathak A, Fourcade J, et al. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. *Eur Heart J*. 2000;21:475-482.
63. Boveda S, Galinier M, Pathak A, et al. Prognostic value of heart rate variability in time domain analysis in congestive heart failure. *J Interv Card Electrophysiol*. 2001;5:181-187.
64. Aronson D, Mittleman MA, Burger AJ. Measures of heart period variability as predictors of mortality in hospitalized patients with decompensated congestive heart failure. *Am J Cardiol*. 2004;93:59-63.
65. Szabo BM, van Veldhuisen DJ, van der Veer N, Brouwer J, De Graeff PA, Crijns HJ. Prognostic value of heart rate variability in chronic congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol*. 1997;79:978-980.
66. Bonaduce D, Petretta M, Marciano F, et al. Independent and incremental prognostic value of heart rate variability in patients with chronic heart failure. *Am Heart J*. 1999;138:273-284.

67. Lucreziotti S, Gavazzi A, Scelsi L, et al. Five-minute recording of heart rate variability in severe chronic heart failure: correlates with right ventricular function and prognostic implications. *Am Heart J.* 2000;139:1088-1095.
68. Miyamoto S, Fujita M, Sekiguchi H, et al. Effects of posture on cardiac autonomic nervous activity in patients with congestive heart failure. *J Am Coll Cardiol.* 2001;37:1788-1793.
69. Sirois BC, Burg MM. Negative emotion and coronary heart disease: a review. *Behav Modif.* 2003;27:83-102.
70. Watkins LL, Grossman P, Krishnan R, Sherwood A. Anxiety and vagal control of heart rate. *Psychosom Med.* 1998;60:498-502.
71. Saul JP, Arai Y, Berger RD, Lilly LS, Colucci WS, Cohen RJ. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. *Am J Cardiol.* 1988;61:1292-1299.
72. Nolan J, Flapan AD, Capewell S, MacDonald TM, Neilson JM, Ewing DJ. Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function. *Br Heart J.* 1992;67:482-485.
73. Szabo BM, van Veldhuisen DJ, Brouwer J, Haaksma J, Lie KI. Relation between severity of disease and impairment of heart rate variability parameters in patients with chronic congestive heart failure secondary to coronary artery disease. *Am J Cardiol.* 1995;76:713-716.
74. Guzzetti S, Cogliati C, Turiel M, Crema C, Lombardi F, Malliani A. Sympathetic predominance followed by functional denervation in the progression of chronic heart failure. *Eur Heart J.* 1995;16:1100-1107.

75. Fei L, Keeling PJ, Sadoul N, et al. Decreased heart rate variability in patients with congestive heart failure and chronotropic incompetence. *Pacing & Clinical Electrophysiology*. 1996;19:477-483.
76. Atherton JJ, Blackman DJ, Moore TD, et al. Diastolic ventricular interaction in chronic heart failure: relation to heart rate variability and neurohumoral status. *Heart Vessels*. 1998;13:269-277.
77. Aronson D, Burger AJ. Gender-related differences in modulation of heart rate in patients with congestive heart failure. *J Cardiovasc Electrophysiol*. 2000;11:1071-1077.
78. Soejima K, Akaishi M, Meguro T, et al. Age-adjusted heart rate variability as an index of the severity and prognosis of heart failure. *Jpn Circ J*. 2000;64:32-38.
79. Malfatto G, Branzi G, Gritti S, et al. Different baseline sympathovagal balance and cardiac autonomic responsiveness in ischemic and non-ischemic congestive heart failure. *European Journal of Heart Failure*. 2001;3:197-202.
80. Musialik-Lydka A, Sredniawa B, Pasyk S. Heart rate variability in heart failure. *Kardiol Pol*. 2003;58:10-13.
81. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, et al. for the Dutch Ibopamine Multicenter Trial Study Group. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. The Dutch Ibopamine Multicenter Trial Study Group. *J Am Coll Cardiol*. 1996;28:1183-1189.
82. Jiang W, Hathaway WR, McNulty S, et al. Ability of heart rate variability to predict prognosis in patients with advanced congestive heart failure. *Am J Cardiol*. 1997;80:808-811.

83. Wijnbenga JA, Balk AH, Meij SH, Simoons ML, Malik M. Heart rate variability index in congestive heart failure: relation to clinical variables and prognosis. *Eur Heart J*. 1998;19:1719-1724.
84. Guzzetti S, Mezzetti S, Magatelli R, et al. Linear and non-linear 24 h heart rate variability in chronic heart failure. *Autonomic Neuroscience-Basic & Clinical*. 2000;86:114-119.

This page left  
blank related to  
a formatting  
issue

TABLE 1 Research that Indicates Heart Failure is Associated With Decreased Heart Rate Variability

| Author/Date                         | Major Purpose of the Study Regarding HRV  | Sample  | Major Findings Related to Heart Rate Variability for Patients with Heart Failure  |
|-------------------------------------|---|---|---|
| Saul et al., 1988 <sup>71</sup>     | Compare the pattern of HRV for patients with severe HF and healthy persons; determine if HRV correlates with hemodynamic and clinical status                  | 25 patients with class III-IV HF; 21 healthy individuals    | Patients with HF had a higher mean HR, lower standard deviation of HR, lower SDNN, and lower spectral power in all frequency bands than healthy individuals; in the 0.04-0.07 Hz band, there was a positive relationship between both absolute and fractional power and cardiac index and an inverse relationship between both absolute and fractional power and PCWP   |
| Binkley et al., 1991 <sup>54</sup>  | Describe the autonomic profile of patients with ventricular dysfunction; evaluate whether patients with ventricular failure have reduced parasympathetic tone | 15 healthy men; 10 patients with congestive cardio-myopathy | Healthy men exhibited both HFP and LFP; patients with HF manifested very little HFP, but amplified LFP; after receiving atropine, healthy persons exhibited a significant decrease in HFP; patients with HF had a lower HF:LF ratio than healthy men; fundamentally, parasympathetic withdrawal is a feature of HF  |
| Nolan et al., 1992 <sup>72</sup>    | Investigate cardiac parasympathetic activity and its association with LV function for patients with HF  | 43 patients with class II-III HF                            | To evaluate parasympathetic activity, HRV was measured by counting the number of times that each RR interval was > 50 ms longer than the preceding RR interval; 60% of patients had lower than expected counts; 24 hour RR counts and LVEF were moderately correlated   |
| Szabo et al., 1995 <sup>73</sup>    | Assess the relationship between severity of HF and changes in HRV   | 79 patients with HF   | NYHA class was inversely correlated with SDNN, SDANN, and LFP; peak VO <sub>2</sub> (ml/min/kg) was positively correlated with SDNN, SDANN, LFP, and HFP; patients with class III-IV HF had lower SDNN, SDANN, and LFP values than patients with class I-II HF; patients with peak VO <sub>2</sub> < 15.9 ml/min/kg had lower SDNN, SDANN, HFP, and LFP values than patients with peak VO <sub>2</sub> > 15.9 ml/min/kg |
| Guzzetti et al., 1995 <sup>74</sup> | Analyze neural activity of the cardiovascular system in patients with HF  | 30 patients with class II-IV HF; 15 healthy individuals     | Patients with class III or IV HF had lower mean RR values than healthy patients and patients with class II HF; patients with class IV HF had higher HFP (nu) values than other patients and healthy persons; LFP (nu) decreased as HF class increased and was nearly absent in patients with class IV HF; when tilted, healthy persons, but not patients with HF, had decreased RR and HFP (nu) and                     |

| Author/<br>Date                         | Major Purpose of the Study<br>Regarding HRV   | Sample   | Major Findings Related to Heart Rate Variability for Patients with<br>Heart Failure   |
|---|---|--|---|
| Fei et al.,<br>1996 <sup>75</sup>       | Evaluate whether the autonomic nervous system contributes to CI in patients with HF   | 41 patients with IDC   | increased LFP (nu) values; only healthy persons had decreased LFP (nu) with controlled respiration  |
| van de Borne et al., 1997 <sup>60</sup> | Examine sympathetic nerve activity for patients with HF   | 21 patients with HF; 12 healthy individuals  | 24% of patients exhibited CI ("an inadequate sinus node response to exercise"); although mean HR was similar, patients with CI had lower SDNN, ln TP, and ln LFP values than patients without CI  |
| Scalvini et al., 1998 <sup>61</sup>     | Use HRV to assess autonomic modulation in patients with HF  | 30 patients with symptomatic class II-IV HF; 21 patients with asymptomatic LVD; 25 healthy individuals | At LFP, patients with HF had lower RR interval variability and MSNA activity than healthy persons; at HFP, patients with HF had higher RR interval variability and MSNA activity than healthy individuals; Only four patients exhibited LFP   |
| Atherton et al., 1998 <sup>76</sup>     | Evaluate whether changes in LVEDV during application of lower-body negative pressure correlate with HRV measures for patients with HF | 30 patients with class I-IV HF   | At rest and during sympathetic and parasympathetic stimulation, patients with HF had lower SDRR and absolute and LFP (nu) values than healthy individuals and patients with LVD; at rest, patients with HF had higher HFP (nu) values than persons in the two other groups; patients with HF and asymptomatic LVD did not manifest HRV changes in response to sympathetic stimulation |
| Yoshikawa et al., 1999 <sup>56</sup>    | Evaluate the relationship among clinical variables, HRV, and baroreceptor sensitivity   | 146 patients with class I-IV HF  | During application of lower-body negative pressure, there was a significant negative correlation between change in LVEDV and SDNN, rmsSD, TP, LFP, and HFP  |
| Aronson & Burger, 2000 <sup>77</sup>    | Explore gender-related differences in HRV for patients with HF  | 131 men and 68 women with class III-IV HF  | Patients were divided into either a high or low norepinephrine group; patients in the high norepinephrine group had lower ln TP, ln LFP, and ln HFP than patients in the low norepinephrine group; TP and LFP were inversely correlated with norepinephrine level; TP was correlated with plasma renin activity; LFP was correlated with baroreceptor sensitivity                     |
|   |   |  | Women had higher SDNN, SDANN, RR, ln ULFP, and ln HFP values than men; for patients with nonischemic HF, women had higher SDNN, SDANN, rmsSD, ln TP, ln ULFP, ln VLFP, ln LFP,  |

| Author/Date                               | Major Purpose of the Study Regarding HRV  | Sample   | Major Findings Related to Heart Rate Variability for Patients with Heart Failure and In HFP values than men   |
|---|---|--|---|
| Soejima et al., 2000 <sup>78</sup>        | Determine whether age-corrected HRV can be used as an index of HF severity and prognosis                                  | 90 patients with class I-IV HF                           | Patients were divided into either a control or a patient group based on their LFP and HFP values; patients with LVD had lower In HFP and In LFP values than controls; control patients had a higher circadian changes of In HFP and LF:HF values; In LFP decreased as HF class increased; in the patient group, HFP did not decrease significantly beyond NYHA class II   |
| Malfatto et al., 2001 <sup>79</sup>       | Evaluate whether the etiology of HF influences the sympathovagal balance and autonomic responsiveness of patients with HF | 21 patients with ischemic HF; 21 patients with IDC       | Patients with ischemic HF had higher LFP (nu) and LF:HF ratio values and lower HFP (nu) values than patients with IDC HF at rest and in response to parasympathetic and sympathetic stimuli; patients with ischemic HF had lower LFP and LF:HF ratio and values during parasympathetic stimulation than at rest   |
| Malave et al., 2003 <sup>3</sup>          | Investigate the relationship between HRV and circulating levels of TNF and norepinephrine                                 | 29 patients with class I-IIIa HF; 10 healthy individuals | Patients with class IIIa HF had lower SDNN, SDAN, In LFP, and HFP values than healthy persons and lower SDNN values than patients with class I-II HF; TNF levels were inversely correlated with SDNN, SDANN, In LFP, and In HFP; norepinephrine levels were inversely correlated with SDNN, SDANN, and In LFP; TNF and In norepinephrine levels predicted SDNN and LFP values                                   |
| Musialik-Lydka et al., 2003 <sup>80</sup> | Analyze HRV in patients with depressed LVEF; relate HRV to clinical parameters  | 105 patients with class II-IV HF; 30 healthy individuals | Patients with HF had lower SDNN, SDANN, and rmsSD values than healthy persons; patients with class III-IV HF had lower SDNN and SDANN values than patients with class II HF; NYNA class was negatively correlated with SDNN, SDANN, and rmsSD values; SDNN and SDANN were moderately correlated with LVEF but were stronger for patients with ischemic cardiomyopathy than patients with dilated cardiomyopathy |

CI = chronotropic incompetence; HF = heart failure; HFP = high frequency power; HR = heart rate; HRV = heart rate variability; IDC = idiopathic dilated cardiomyopathy; LFP = low frequency power; In = logarithmic units; nu = normalized units; LV = left ventricular; LVD = left ventricular dysfunction; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; mean RR = mean duration of all normal to normal (NN) RR intervals; MSNA = muscle sympathetic nerve activity; NYHA = New York Heart Association; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; peak VO<sub>2</sub> = peak oxygen consumption;

pNN50 = percentage of adjacent normal RR intervals > 50 ms different; PVC = premature ventricular contraction; rmsSD = square root of the mean of the squares of differences between adjacent RR intervals; SDNN = standard deviation of all normal RR intervals; SDANN = standard deviation of the averages of RR intervals in all 5-minute segments; SNS = sympathetic nervous system; TNF = tumor necrosis factor; TP = total power; ULFP = ultra-low frequency power; VLFP = very low frequency power

TABLE 2 Research That Indicates Decreased Heart Rate Variability is Associated With Poor Outcomes

| Author/Date                           | Major Purpose of the Study Regarding HRV  | Sample                                       | Major Findings Related to Heart Rate Variability for Patients with Heart Failure   |
|---------------------------------------|---|--|--|
| Brouwer et al., 1996 <sup>81</sup>    | Determine the prognostic value of HRV for patients with mild to moderate HF   | 95 patients with chronic class II-III HF     | No relationship between time and frequency HRV measures and mortality; in a multivariate model, abnormal HRV Poincaré plots independently predicted <i>all-cause cardiac death</i> and <i>SCD</i>  |
| Ponikowski et al., 1997 <sup>35</sup> | Evaluate the prognostic value of HRV for patients with moderate to severe HF  | 102 patients with class II-IV HF             | In a multivariate model, SDNN, SDANN, and LFP predicted <i>cardiac mortality</i> independently of peak $\dot{V}O_2$ , NYHA class, LVEF, and VT; patients with a SDNN < 100 ms had higher 1-year mortality rates than patients with a SDNN > 100 ms   |
| Fauchier et al., 1997 <sup>34</sup>   | Assess the relationship between HRV and hemodynamic variables and ventricular dysrhythmias for patients with IDC; investigate the prognostic value of HRV | 93 patients with IDC; 63 healthy individuals | Patients with IDC had a lower mean RR, SDNN, rmsSD, and day HR:night HR ratio than healthy persons; patients with IDC and class II-IV HF, had a lower mean RR, SDNN, and day HR:night HR ratio than patients with class I HF; mean RR, SDNN, and day HR: night HR ratio correlated with LV shortening fraction, PCWP, and LVEF; in multivariate analysis, decreased SDNN independently predicted <i>future cardiac events</i> ; SDNN < 100 was associated with <i>higher mortality</i> rates |
| Szabo et al., 1997 <sup>65</sup>      | Assess the prognostic value of HRV for patients with HF   | 159 patients with class II-IV HF             | In a multivariate model, decreased SDNN and pNN50 predicted <i>all-cause mortality</i> ; pNN50 < 2% and LFP > 14 ms <sup>2</sup> predicted <i>death from progressive pump failure</i>  |
| Jiang et al., 1997 <sup>82</sup>      | Assess the ability of HRV to predict mortality and life-threatening cardiac events for patients with HF   | 26 patients with $\geq$ IIIb HF              | Patients who <i>died</i> or had a <i>life-threatening event</i> had lower SDNN and SDANN values than patients without events; SDNN $\leq$ 53.4 ms and SDANN $\leq$ 41.3 ms were associated with shorter <i>event-free survival</i> ; other clinical measures did not distinguish event-free patients from those who had cardiac events   |
| Nolan et al., 1998 <sup>36</sup>      | Assess the prognostic value of HRV for patients with HF   | 433 patients with class I-III HF             | SDNN was a univariate and multivariate predictor of <i>all-cause mortality</i> ; patients with SDNN < 50 msec had highest mortality rates; SDNN was a stronger predictor of <i>death</i> related to progressive HF than other conventional clinical parameters   |
| Wijbenga et al.,                      | Assess the clinical and prognostic value of HRV for patients with HF  | 64 patients with HF                          | HRVI was positively associated with LVEF and deceleration time; in a multivariate model that included several clinical parameters,   |

| Author/Date                            | Major Purpose of the Study Regarding HRV   | Sample   | Major Findings Related to Heart Rate Variability for Patients with Heart Failure   |
|--|--|--|--|
| 1998 <sup>83</sup>                     |  |  | HRV index independently predicted <i>cardiac death</i> and <i>heart transplantation</i>  |
| Bonaduce et al., 1999 <sup>66</sup>    | Assess the predictive value of HRV for patients with HF  | 97 patients with HF  | Patients with class III-IV HF had lower time domain (mean RR, SDNN, SDANN index, SDNN index) and frequency domain (ln TP, ln ULFP, ln VLFP, ln LFP, LF:HF ratio) measures of HRV than patients with class II HF; SDNN, SDANN index, pNN50, and LF:HF ratio predicted <i>mortality</i> for patients regardless of etiology; the inclusion of HRV data improved the prognostic value of clinical and echocardiographic data      |
| Guzzetti et al., 2000 <sup>84</sup>    | Determine the prognostic value of spectral and non-linear analysis of HRV  | 30 patients with HF; 20 healthy individuals                  | Compared to healthy persons, patients with HF had lower LF (nu) and LF:HF values, higher HFP (nu) values, and a steeper 1/f slope; baseline LFP (absolute and nu) was higher and the 1/f slope less steep for patients who were <i>alive</i> at 15-month follow-up   |
| Galinier et al., 2000 <sup>62</sup>    | Assess the prognostic value of HRV for all-cause and sudden death  | 190 patients with class II-IV HF                             | Non-survivors had lower SDNN, SDANN, SD, in day-time and in night-time TP, in day-time and in night-time LFP, and in night-time HFP values; in a multivariate model, SDNN predicted <i>all-cause death</i> while day-time ln LFP predicted <i>sudden death</i>   |
| Lucreziotti et al., 2000 <sup>67</sup> | Assess the interaction between autonomic activity and RV function in severe HF and determine whether this predicts future cardiac events | 75 patients with severe HF                                   | The LF:HF ratio was inversely correlated with norepinephrine levels; in a multivariate model that included standard clinical variables, only low LF:HF ratio independently predicted <i>cardiac death</i> and <i>heart transplantation</i> ; TP and LFP were positively correlated with RVEF; HFP was inversely associated with RVEF   |
| Makikallio et al., 2001 <sup>1</sup>   | Evaluate whether HRV predicts mortality for patients with chronic HF with ventricular dysfunction  | 499 patients with class II-IV HF and ventricular dysfunction | Mean HR, SDNN, HRVI, VLFP, and short-term fractal exponent ( $\alpha_1$ ) were univariate predictors of <i>mortality</i> ; HRV indices were stronger univariate predictors of <i>mortality</i> for patients with class II HF than for those with class III or IV HF; after adjusting for other risks such as age and L V function, $\alpha_1$ predicted <i>mortality</i> for patients with class II but not class III or IV HF |
| Boveda et al., 2001 <sup>63</sup>      | Assess the prognostic value of time domain measures of HRV for patients with HF  | 190 patients with class II-IV HF                             | Survivors had higher SDNN, SDANN, and SD values; in a multivariate model, SDNN independently predicted <i>all-cause death</i>  |

| Author/<br>Date           | Major Purpose of the Study<br>Regarding HRV   | Sample   | Major Findings Related to Heart Rate Variability for Patients with<br>Heart Failure  |
|---------------------------|---|--|--|
| Bilchick et<br>al., 2002  | Evaluate whether HRV could<br>predict SCD in patients with HF   | 127 patients<br>with class II-IV<br>HF   | Patients with SDNN < 65.3 msec had a higher risk of <i>mortality</i> and<br>SCD than patients with SDNN $\geq$ 65.3 msec; in a multivariate<br>model containing demographic and clinical variables, only SDNN<br>predicted overall <i>mortality</i>                  |
| La Rovere<br>et al., 2003 | Determine whether HRV predicts<br>SCD for patients with HF  | Derivation and<br>validation<br>samples of 202<br>and 242<br>patients,<br>respectively,<br>with moderate<br>to severe HF | For the derivation sample, lower LFP during controlled breathing<br>and LVEDD independently predicted SCD; in the validation<br>sample, lower LFP during controlled breathing and number of<br>PVCs/hour predicted SCD   |
| Aronson et<br>al., 2004   | Investigate whether HRV<br>measures predict post-discharge<br>survival for patients admitted with<br>decompensated HF | 199 patients<br>with class III-<br>IV HF   | In a multivariate model, patients with SDNN, SDANN, TP, and<br>ULFP values < 44 ms, < 37 ms, < 1,475 ms <sup>2</sup> , and < 1,100 ms <sup>2</sup><br>respectively, had higher <i>mortality</i> rates; ULFP power was the<br>strongest predictor of <i>mortality</i> |

Refer to Table 1 for abbreviations; also HRVI = heart rate variability index; LVEDD = left ventricular end-diastolic diameter; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; SD = mean of the standard deviations of all RR intervals for all 5-minute segments; VT = ventricular tachycardia

## Figure Legends

Figure 1: Beat-by-beat heart rate over time from an individual patient. "Cardiotachometer" output shown here resulted from the computer detecting the interval between onset of successive individual heart beats and converting the resultant sequence of RR intervals into visual display of heart rate. Heart rate fluctuated significantly from moment-to-moment. Power spectral analysis is a mathematical process that quantitatively summarizes these fluctuations in terms of frequency and amplitude.

Figure 2: Arterial blood pressure (top, mm HG; recorded non-invasively), RR interval (middle, msec.) and ECG (bottom) show waxing and waning of inter-beat interval over time in this resting subject. This arrhythmia, which originates in sinus node (note P waves preceding each QRS complex) and is in phase with respiration, is known as respiratory sinus arrhythmia. This rhythm appears in the heart rate power spectrum within the "high frequency" region and is mediated by alterations in parasympathetic nervous activity to the SA-node.

Figure 3: Illustrative heart rate power spectrum from an individual patient. Ordinate is power ( $\text{mm Hg}^2$ ) shown here using a linear scale; abscissa is frequency (Hz). High frequency (HF) peak at respiratory rate is widely acknowledged to be under the control of the parasympathetic nervous system, though the precise relationship between changes in cardiac vagal nervous activity and changes in HF power has not been established. Low frequency (LF) peak typically occurs at about 0.1 Hz in the human; the power within the HF region in the heart rate spectrum appears to be jointly controlled by cardiac sympathetic and parasympathetic nervous activity. The very low frequency (VLF) peak has been attributed to slowly varying changes in vasomotor tone, probably related to processes such as thermoregulation.

Figure 1.

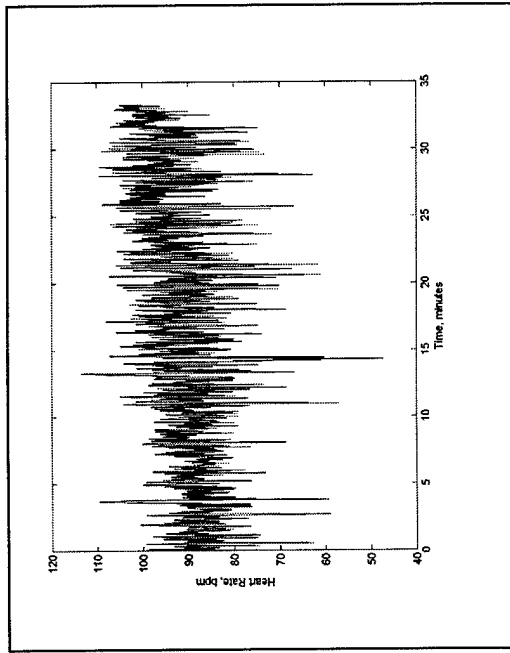


Figure 2.

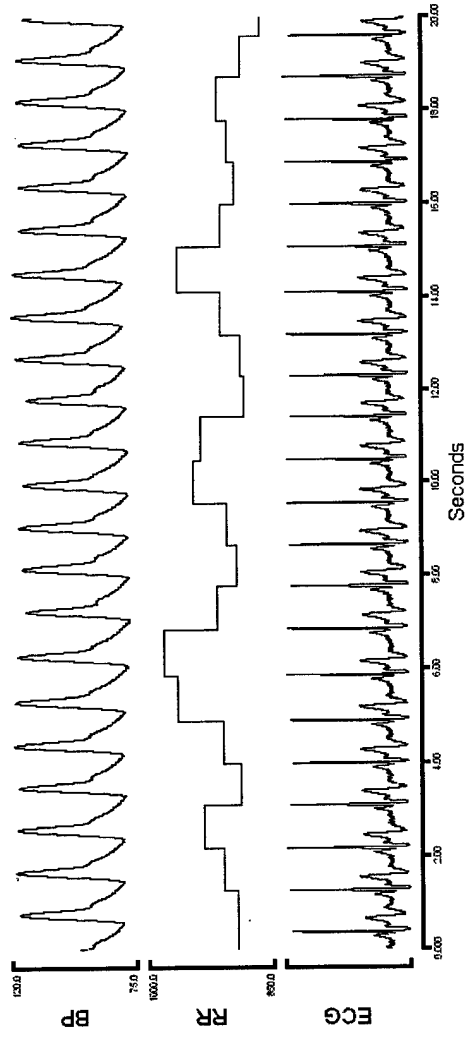


Figure 3.

