Psychophysiology, 34 (1997), 623–648. Cambridge University Press. Printed in the USA.

COMMITTEE REPORT

Heart rate variability: Origins, methods, and interpretive caveats

GARY G. BERNTSON,[a] J. THOMAS BIGGER, JR.,[b] DWAIN L. ECKBERG,[c] PAUL GROSSMAN,[d] PETER G. KAUFMANN,[e] MAREK MALIK,[f] HAIKADY N. NAGARAJA,[g] STEPHEN W. PORGES,[h] J. PHILIP SAUL,[i] PETER H. STONE,[j] AND MAURITS W. VAN DER MOLEN[k]

[a]Department of Psychology, Ohio State University, Columbus, USA
[b]Columbia University, New York, USA
[c]Medical College of Virginia, Richmond, VA, USA
[d]Lown Cardiovascular Center, Brookline, MA, USA
[e]Division of Epidemiology and Clinical Applications, National Heart Lung & Blood Institute, Bethesda, MD, USA
[f]Department of Cardiological Sciences, St. George's Hospital Medical School, London, UK
[g]Department of Statistics, Ohio State University, Columbus, USA
[h]Institute for Child Study, University of Maryland, College Park, USA
[i]Children's Hospital, Boston, MA, USA
[j]Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
[k]Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands

Abstract

Components of heart rate variability have attracted considerable attention in psychology and medicine and have become important dependent measures in psychophysiology and behavioral medicine. Quantification and interpretation of heart rate variability, however, remain complex issues and are fraught with pitfalls. The present report (a) examines the physiological origins and mechanisms of heart rate variability, (b) considers quantitative approaches to measurement, and (c) highlights important caveats in the interpretation of heart rate variability. Summary guidelines for research in this area are outlined, and suggestions and prospects for future developments are considered.

Descriptors: Autonomic nervous system, Cardiac chronotropic control, Electrocardiogram, Heart rate, Methodology, Parasympathetic, Respiratory sinus arrhythmia, Sympathetic, Vagal tone

Measures of heart rate variability are increasingly being employed in applications ranging from basic investigations of central regulation of autonomic state, to studies of fundamental links between psychological processes and physiological functions, to evaluations of cognitive development and clinical risk. As psychological correlates and physiological mechanisms are being delineated, measures of heart rate variability may offer powerful tools for the clarification of relationships between psychological and physiological processes. At the same time, there are clear caveats and pitfalls in the measurement, analysis, and interpretation of heart rate variability. Although patterns of heart rate variability hold considerable promise for clarifying issues in psychophysiology, the inappropriate quantification and interpretation of these patterns may obscure critical issues or relationships and may impede rather than foster the development of psychophysiological applications. The ultimate utility and general scientific acceptance of measures of heart rate variability will undoubtedly depend on the extent to which researchers from diverse disciplines are able to formulate an integrative and interdisciplinary perspective on the origins, quantification, and interpretation of patterns of heart rate variability. The present report is intended to promote that end and to establish general standards and guidelines for psychophysiological applications of heart rate variability measures.

A recent report of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force, 1996) represents an important step toward standardization of the field. The present document focuses on research applications and is intended to extend rather than supplant the previous report. Physiological origins and mechanisms of periodic components of heart rate variability are considered first. Quantitative approaches to the measurement of heart rate variability are then discussed, followed by considerations and caveats in the interpretation of these measures. Finally, summary guidelines for research in this area are outlined, and suggestions and prospects for future developments are considered.

Historical Overview

Long before the invention of the electrocardiograph and the more recent emergence of modern constructs of heart rate variability, physicians recognized the potential importance of cardiac rhythms. Techniques for studying heart rate patterns were limited prior to

Address reprint requests to: Dr. Gary G. Berntson, Department of Psychology, Ohio State University, 1885 Neil Avenue, Columbus, OH 43210, USA. E-mail: berntson.2@osu.edu.

this century, but for several hundred years physicians have monitored heart sounds and rhythms by auscultation and have noted beat-to-beat rhythm shifts associated with aging, illness, and psychological states. The study of these rhythms became a central component of medical diagnostic systems developed in China. The scientific investigation of beat-to-beat heart rate rhythms, however, awaited technological advances that enabled accurate and reliable quantification of the electrical activity of the heart. This technology has progressed from the galvanometer, to the kymograph, to the inkwriting polygraph, and finally to digital signal processing systems.

The early work of Luigi Galvani and Alessandro Volta and the electromagnetic principles articulated by André-Marie Ampère and Hans Christian Oersted led to the development of the galvanometer in the 19th century. This device permitted the measurement of very small electrical currents by capitalizing on magnetic induction to rotate a pointer or mirror. The galvanometer could be calibrated to measure accurately changes in voltage, including biopotentials generated by the heart. Ludwig (1847) subsequently invented the smoked kymograph, which allowed mechanical activity, such as that associated with pressure pulses or the movement of a galvanometer needle, to be recorded on a smoked drum. In 1894, MacKenzie developed an ink-writing polygraph (see MacKenzie, 1910), and Einthoven integrated the galvanometer with photography to produce accurate and continuous tracings of the electrical activity of the heart (see Erschler, 1988). With the development of the electrocardiograph, it was possible to monitor normal and abnormal electrical conduction through the myocardium and to evaluate beat-to-beat changes in the heart rate pattern.

It could be argued that the origins of the scientific study of heart rate variability predate the development of the electrocardiograph. The first documented observation of heart rate variability is often credited to Hales (1733), who observed a respiratory pattern in the blood pressure and pulse of a horse. By means of the kymograph, Ludwig (1847) was able to observe a regular quickening of pulse rate with inspiration and a slowing with exhalation in the dog. This may be the first documented report of respiratory sinus arrhythmia (RSA), and the subsequent work of Donders (1868) focused attention on the relations among respiration, heart rate, and the vagus nerve. Two potential physiological origins were proposed for RSA in the second half of the 19th century (see Anrep, Pascual, & Rössler, 1936a). In 1865, Traube speculated that the brainstem nuclei controlling heart rate might be influenced phasically by direct "irradiations" from the medullary respiratory centers (see Anrep et al., 1936a). Recent neuroanatomical and neurophysiological data support a contemporary version of this model that emphasizes the interneuronal communication between brainstem networks in generating a common cardiopulmonary frequency (Richter & Spyer, 1990). An alternative explanation was offered in 1871 by Hering, who proposed that reflex modulation of the cardioregulatory centers by pulmonary afferent feedback may be the physiological mechanism underlying RSA. References to RSA were made in several scientific sources during the early 1900s. There is mention of RSA even in early psychology textbooks, although its origins were not understood at the time. Wundt (1902) stated that "the movements of the lungs: their inflation accelerates, their collapse reduces the frequency of heart beat. The respiratory movements are therefore regularly accompanied by fluctuations of the pulse, whose rapidity increases in inspiration and decreases in expiration" (p. 247).

Several historical studies highlight the emergence of heart rate variability as a physiologically meaningful measure. Most of these early clinical and physiological studies focused on RSA. In fact, in early research there is little distinction between a global concept of sinus arrhythmia and the more specific rhythmicity of RSA. Research on heart rate variability moved initially in two directions. First, there was a dominant trend toward understanding the physiological mechanisms mediating heart rate rhythms. Second, medical researchers identified specific relationships between heart rate variability and clinical status. Later, with the availability of polygraphs in academic laboratories in the 1960s, a third trend appeared as psychophysiologists began to investigate the relationship between psychological processes and heart rate variability.

An example of early physiological research on heart rate variability is a report by Bainbridge (1920) that sought to explain RSA in terms of alterations in baroreceptor and volume receptor responses associated with respiratory alterations in thoracic pressure. Anrep, Pascual, and Rössler (1936a, 1936b) examined alternative explanations of the physiological mechanisms of RSA in what appears to be the first extensive and systematic study of RSA. A functional relation between the amplitude of RSA and the concept of vagal tone was suggested early in this century by Hering (1910), who stated that "it is known with breathing that a demonstrable lowering of heart rate . . . is indicative of the function of the vagi."

Eppinger and Hess (1915) provided a starting point for the clinical trend. They asserted that "clinical facts, such as respiratory arrhythmia, habitual bradycardia, etc., have furnished the means of drawing our attention to the variations in the tonus of the vagal system in man" (p. 12). The case studies of Eppinger and Hess focused on clinical problems related to putative abnormalities in the regulation of autonomic functions. Their observations were important because they drew attention to the potential role of the autonomic nervous system in atypical physiological responses and clinical disorders and focused on possible relationships between individual differences in physiology and psychiatric pathology. Their studies also emphasized the sensitivity of the vagus to cholinergic substances, which might allow for pharmacological manipulations and potential treatments.

Clinical research interests in RSA were rekindled in cardiology by the early work of Wolf (1967) and in obstetrics and gynecology by Hon (Hon, 1958; Hon & Lee, 1963). Both Hon and Wolf emphasized the relationship between heart rate variability and nervous system status. Hon treated heart rate variability as a global index of fetal distress. Wolf, with a focus on the contribution of central nervous system factors to sudden cardiac death, viewed heart rate variability as reflecting brain–vagal–heart communication. Wolf's theoretical interest in brain–heart relations provided an important bridge between clinical research and psychophysiology.

Psychophysiology has been at the crossroads of different models and strategies for research. Unlike physiology, with its primary interest in mechanisms, or cardiology, with its principal interest in clinical status, psychophysiology has been driven by paradigms derived from psychology, focusing on physiological parameters that relate to psychological and behavioral states. Early psychophysiological studies of heart rate generally viewed the beat of the heart as a dependent variable that was causally influenced by cognitive (e.g., Lacey, 1967) and metabolic (e.g., Obrist, 1981) processes. At that time, heart rate variability was sometimes viewed as error variance attributable to poor experimental control or to the incomplete specification of contextual determinants of heart rate.

As heart rate variability began to be recognized as an interesting and potentially important phenomenon, it was treated largely as a descriptive variable without attributing it to any specific physiological mechanism. Previous studies have reflected three general

perspectives: (a) an individual difference model treating heart rate variability as a traitlike variable that is predisposed toward predictable patterns of behavioral and autonomic response (e.g., Lacey & Lacey, 1958; Porges, 1972; Price, 1975; Thackray, Jones, & Touchstone, 1974), (b) the measurement of heart rate variability as an index of attention, mental effort, or mental load (e.g., Kahneman, 1973; Kalsbeek & Ettema, 1963; Lacey, 1967; Porges & Raskin, 1969; Sayers, 1973), and (c) the stimulus control of heart rate variability by operant conditioning or biofeedback techniques (Hnatiow & Lang, 1965; Lang, Sroufe, & Hastings, 1967).

The specific issues and questions within these disparate lines of development were often quite distinct, which did not always foster interdisciplinary perspectives. Currently, there is increasing recognition that quantification and interpretation of heart rate variability depend not only on an adequate appreciation of the underlying physiological mechanisms but also on the interactions between these mechanisms and behavioral processes.

Empirical Foundations

Components and Origins of Heart Rate Variability

Periodic components of heart rate variability tend to aggregate within several frequency bands. In young healthy individuals at rest, the most conspicuous of these bands is at the respiratory frequency (RSA). The respiratory frequency band is considered to range (nominally) from about 0.15 Hz to 0.4 Hz in humans but may extend below 0.15 Hz and up to 1 Hz or more for infants and for adults during exercise. RSA is generally believed to be mediated predominately by fluctuations of vagal–cardiac nerve traffic and thus may provide an index of vagal activity. R–R interval oscillations[1] also occur at *low* frequencies (about 0.05–0.15 Hz), including a 0.1-Hz component that is sometimes referred to as the *10-s rhythm* or the *Mayer wave* (Mayer, 1877; Penáz, 1978). This frequency range has been termed the *mid*-frequency band by some authors (e.g., Mulder, 1985, 1992),[2] but the designation of *low* frequency (LF) is more common and is used in the present report. The LF heart rate rhythms have been suggested to reflect mainly sympathetic outflow (Malliani, Pagani, Lombardi, & Cerutti, 1991; Malliani, Pagani, & Lombardi, 1994) but are thought by most investigators to be of both sympathetic and vagal origin (Akselrod et al., 1985; Koh, Brown, Beightol, Ha, & Eckberg, 1994; Pomeranz et al., 1985).

Other R–R interval fluctuations occur at frequencies below 0.05 Hz. These have been designated variously (see Footnote 2), but commonly used bands include *very low* frequencies (VLFs; about 0.003–0.05 Hz) and slower, *ultra low* frequencies (ULFs) that include circadian rhythms. The VLF R–R interval oscillations have been studied much less than higher frequency rhythms and may reflect thermoregulatory cycles (Kitney, 1980; Sayers, 1973) or fluctuations related to plasma renin activity (Akselrod et al., 1981; Bonaduce et al., 1994). Circadian heart rate variability reflects a wide range of determinants, including changes of activity, posture, breathing, autonomic outflow, state of arousal, and a range of behavioral variables. Although VLF or slower rhythms of heart rate may have important clinical applications (Malik, Farrell, & Camm, 1990) and psychophysiological correlates (e.g., Mulder, 1992), they will not be considered because their origins and mechanisms remain unclear.

Autonomic and Nonautonomic Control of the Heart

The normal rhythm of the heart is controlled by membrane processes of the cardiac sinoatrial (SA) node, which are modulated by innervation from both the sympathetic and parasympathetic divisions of the autonomic nervous system (for recent reviews, see Burkholder et al., 1992; Levy & Warner, 1994; Randall, 1994). Acetylcholine, released by postganglionic parasympathetic terminals at the sinoatrial node, slows the rate of SA node depolarization and discharge by binding to muscarinic cholinergic receptors and activating a transmembrane potassium channel. In contrast, norepinephrine is released by sympathetic terminals on the SA node and speeds the SA node rhythm via a β_1 receptor-mediated second messenger cascade of intracellular signals. In addition to these classic neurotransmitter actions, the chronotropic state of the heart can be modulated by a variety of neuropeptides, such as neuropeptide Y, that appear to be colocalized with conventional neurotransmitters in autonomic terminals (Hill, Wallick, Martin, & Levy, 1995; Shine, Potter, Biden, Selbie, & Herzog, 1994).

Although chronotropic control of the heart is attributable largely to direct autonomic innervation of the SA node, other factors can influence heart rate. In addition to its direct neural innervation of the heart, the sympathetic system can modulate heart rate indirectly through the release of adrenomedullary catecholamines. Other humoral factors that may influence heart rate variability include variations in the activity of the renin-angiotensin system (Akselrod et al., 1981; Bonaduce et al., 1994). Humoral influences on heart rate variability are apparent even after cardiac denervation. Cardiac transplant patients, for example, show LF heart rate variations that are probably attributable primarily to humoral effects and small, residual higher frequency fluctuations that are likely due to respiratory-related mechanical stretch of the sinoatrial node.

Cardiac efferent control: Dynamic and steady-state effects. Both dynamic and steady-state characteristics of the cardiac response to vagal and sympathetic activity have been studied extensively. Parker, Cellar, Potter, and McCloskey (1984) demonstrated that the steady-state increase in heart period to vagal stimulation at frequencies between 1 and 30 Hz was almost perfectly linear in the dog. Additional studies in a number of mammalian species have yielded similar results (Berger, 1987; Berntson, Quigley, Fabro, & Cacioppo, 1992; Rosenblueth & Simeone, 1934), although the response of human hearts may plateau at higher stimulation frequencies (Carlson et al., 1992; Carlsten, Folkow, & Hamberger, 1957; for review, see Berntson, Cacioppo, & Quigley, 1995). Parallel studies of sympathetic stimulation have revealed less linear effects on steady-state decreases in heart period, with diminishing effects at frequencies above 1.5–2 Hz and saturation (i.e., a ceiling effect) at higher frequencies in dogs and cats (Berger, 1987; Levy & Zieske, 1969; Rosenblueth & Simeone, 1934).

Because respiratory and slower rhythms are apparent in the activity of both branches of the autonomic nervous system, studies of the functional effects of phasic modulation of sympathetic and vagal activities are especially pertinent to patterns of heart rate

[1]The time between heart beats is variously designated as heart period, R–R interval, or interbeat interval. Heart period is a more abstract representation that is not tied to any specific starting point or measurement interval, whereas R–R interval more closely corresponds to what is actually measured in most cases.

[2]Mulder (1985, 1992) also identified a more restricted low frequency band extending from 0.02–0.06 Hz that overlaps with the low frequency (0.05–0.15 Hz) and the very low frequency bands (0.0033–0.05), as used here. Other differences among researchers also exist in the designation of frequency band. Malliani, Pagani, Lombardi, and Cerutti (1991) and Malliani, Pagani, and Lombardi (1994), for example, considered the very low frequency band to extend down to DC and did not differentiate the ultra low frequency band as considered in the present paper.

variability and psychophysiological responses of the heart (de Boer, Karemaker, & Strackee, 1985; Somsen, Molenaar, van der Malen, & Jennings, 1991). These studies reveal that the cardiac response to vagal activity is rapid, whereas that to sympathetic activity is characterized by a pure time delay and a slower response. Spear, Kronhaus, Moore, and Kline (1979) examined heart period responses to brief bursts of sympathetic and vagal activity. Results, which simulate an impulse response, demonstrated that a vagal burst had its maximum effect at approximately 0.5 s, with a return to baseline within 1 s, followed by a slower rebound in the direction of decreasing R–R intervals. A sympathetic burst caused no effect for approximately 1 s, maximum decrease in R–R intervals at about 4 s, and a return to baseline within 20 s. These impulse response results were virtually identical to those found by Berger, Saul, and Cohen (1989) and Penáz (1962) using frequency-domain techniques. Both vagal and sympathetic responses were characteristic of low-pass filters, with the addition of a delay in the case of the sympathetic response. The vagal filter had a corner frequency of 0.15 Hz, with the gain falling to about 80% of direct current (DC) by 0.5 Hz. Berger et al. (1989) also found that the response characteristics and particularly the corner frequency varied slightly as a function of the mean vagal stimulation frequency. At lower stimulation frequencies, the DC intercept was larger and the corner frequency lower than at higher frequencies. Berger (1987) also examined the response of the sinus node to modulation of sympathetic activity. In accord with the more dampened impulse response characteristics found by Spear et al. (1979), the sympathetic frequency response had a corner frequency of 0.015 Hz, which is consistent with a low-pass filter, and showed a pure time delay of about 1.7 s. Berger also determined the impulse response characteristics from the frequency responses and found functions that were virtually identical to those reported by Spear et al. (1979). In summary, vagal responses are faster with little delay, whereas sympathetic responses are slower with a 1–2-s time delay.

The differences in delay of the cardiac response to sympathetic and vagal activation appear to relate largely to receptor processes and postsynaptic responses. Hill-Smith and Purves (1978) determined that the response characteristics were not due to differences in diffusion at the muscarinic or adrenergic receptors. Iontophoretic delivery of either acetylcholine or norepinephrine to within 5 μ of the cell surface suggested that the delay in the cardiac response to these neurotransmitters probably arose from processes subsequent to the binding of the agonist to the receptor. Consistent with this interpretation, Hille (1992) demonstrated that the linkage between muscarinic receptor activation and changes in ionic currents is mediated by signaling molecules located largely within the cell membrane. In contrast, adrenergic stimulation is initiated in the membrane, and it requires second-messenger activation of a protein kinase in the cytosol, which eventually sends a signal back to the membrane to change ionic currents in Phase 4 depolarization (Hille, 1992). These features and the differences in the rate of termination of receptor action (Levy, Yang, & Wallick, 1993) appear to underlie differences in the time constants of the vagal and sympathetic responses.

Fewer data are available for peripheral sympathetic responses. Rosenbaum and Race (1968) demonstrated that the frequency response characteristics of vascular resistance vessels by modulation of sympathetic activity were virtually identical to those found for the atrial rate responses by Berger et al. (1989). That is, the corner frequency of the response was about 0.01–0.02 Hz, and the phase characteristics suggested both a low-pass filter and a time delay. Thus, sympathetic responses in both the periphery and the heart have similar characteristics, with a 1–2-s pure time delay and a corner frequency of about 0.015 Hz. Vagal cardiac responses have a much shorter delay and a corner frequency of about 0.15 Hz. These findings are consistent with the observations in humans that the parasympathetic nervous system is able to modulate heart rate effectively at all frequencies between 0 and 0.5 Hz, whereas the sympathetic system modulates heart rate with significant gain only below 0.1 Hz.

Hormonal and nonautonomic influences. There are relatively few quantitative data describing either the time-domain or frequency-domain responses of heart rate to hormonal modulation. The best indications can probably be surmised from the heart rate variability characteristics of cardiac transplant patients. Early after transplant, prior to evidence of sympathetic reinnervation, resting supine patients show little or no heart rate variability (Bernardi et al., 1989, 1990; Sands et al., 1989; Shapiro, Sloan, Bagiella, Bigger, & Gorman, 1996). The exception is a small mechanically mediated RSA. With exercise and during 24-hr ambulatory activity, however, transplant patients are able to modulate heart rate at very low frequencies (Arai et al., 1989; Bernardi et al., 1989; Saul et al., 1992). The time constants of the heart rate responses suggest that hormonal heart rate control is active only at frequencies below about 0.03 Hz.

A small RSA of approximately 2 bpm per liter of respiration persists even after combined pharmacologic cardiac sympathetic and vagal blockade (Cacioppo et al., 1994; Saul et al., 1991) and after cardiac transplantation (Bernardi et al., 1989, 1990). These findings indicate that at least part of RSA has an intracardiac origin; either an intracardiac reflex or a mechanical stretch of the sinoatrial node may be involved. Stretch-induced changes in SA node rate have been documented experimentally in animals (James, 1973; Koizumi, Ischikawa, Nishono, & Brooks, 1975), but the magnitude of these responses is difficult to compare with those from normal humans. Saul et al. (1991) found that the transfer relation between respiration and heart rate after complete autonomic blockade had features that were qualitatively similar to those of a positive differentiator, suggesting that nonautonomic RSA may be related to the rate of change of lung volume. This idea is consistent with an atrial stretch mechanism because respiratory air flow is related to the intrathoracic pressure changes that drive changes in atrial size (West & van Vleit, 1983). Bernardi et al. (1989) reached a similar conclusion from studies of heart transplant recipients. Thus, in the absence of autonomic heart rate control, a relatively small effect of SA node stretch may become evident.

Heart Rate Variability at Respiratory Frequencies

Autonomic afferents continually convey information regarding the state of the circulation to the nucleus tractus solitarius (Felder & Mifflin, 1994), and this afferent input can modulate autonomic outflows via potent brainstem reflexes. Baroreceptor reflexes, for example, exert powerful inhibitory influences on sympathetic outflow and provide an important source of excitatory drive to vagal motoneurons. Baroreceptor reflexes are particularly relevant to the study of heart rate variability because these reflexes can operate phasically within the rapid time frame of even the highest frequency heart rate rhythms. Kezdi and Geller (1968) found that pressure oscillations in the carotid sinus of up to at least 1 Hz were accurately reflected in baroreceptor afferents, which is well beyond the corner frequencies of the autonomic innervations of the heart. Thus, baroreceptor afferents are able to transmit accurately arterial pressure fluctuations up to the highest frequency ranges of

heart rate variability. Baroreflex manifestations at the end organ are slowed somewhat by delays in central reflex networks and by the added time for neural transmission and neuroeffector transduction. For brief arterial baroreceptor stimulation in human individuals, the minimum reflex latency is about 0.25 s, the time-to-peak effect is about 2.5 s, and the decay of the response is about 2.0 s (Eckberg, 1976, 1980; Eckberg & Eckberg, 1982; see also Borst & Karemaker, 1983). These values are compatible with a substantive contribution of baroreceptor reflexes in RSA (for review, see Eckberg, 1995).

Reflex networks of the nucleus tractus solitarius in turn are modulated by respiratory influences of both central and peripheral origin, and sympathetic and vagal nerve activities fluctuate on a breath-by-breath basis. Because baroreceptor afferents modulate activities of spinal sympathetic and medullary vagal motoneurons, respiratory modulation of autonomic nerves is proportional to basal levels of activity in those nerves (Eckberg et al., 1988). Respiration gates the effects of afferent inputs on muscle sympathetic (Eckberg, Nerhed, & Wallin, 1985) and vagal (Eckberg, Kifle, & Roberts, 1980; Eckberg & Orshan, 1977) motoneurons. At usual breathing frequencies, autonomic sensory inputs are more likely to influence sympathetic and vagal firing when they arrive during expiration than at inspiration. Respiratory modulation is finite, however, because gating of vagal firing is nearly maximal at typical levels of arterial baroreceptor stimulation and disappears at low and high levels of baroreceptor activation (Anrep et al., 1936a; Eckberg et al., 1988; Eckberg & Orshan, 1977). Thus, baroreflex modulation of autonomic control is characterized by clear asymptotes at both extremes of activity (Eckberg, 1995).

Respiratory–frequency rhythms in autonomic nerves are translated into changes in discharge frequency of the SA node; thus, RSA frequency differs with breathing rate. Because of the low-pass-filter characteristics of the autonomic–cardiac innervations, however, RSA can be substantially greater during slow than during fast breathing, although average R–R intervals over a wide range of breathing frequencies may remain nearly constant (Brown, Beightol, Koh, & Eckberg, 1993; Grossman, Karemaker, & Wieling, 1991). Saul et al. (1991) found that the transfer function relating respiration to RSA had frequency characteristics nearly identical to those for direct vagal stimulation. In the aggregate, these findings suggest that, at slow breathing frequencies, the phasic vagal cholinergic influence on the SA node has sufficient time to achieve full effect and dissipate. At more rapid breathing frequencies, however, responses to successive cycles of cholinergic action begin to merge, and phasic SA responses decrease in amplitude.

The slower dynamics of sympathetic actions at the SA node limit sympathetic contributions to respiratory modulations of heart rate variability. Saul et al. (1991, 1992) found that the sympathetic component of RSA (apparent only at frequencies below 0.15 Hz) and the response to random binary neck chamber stimulation were nearly identical to those found by Rosenbaum and Race (1968) for the peripheral vascular receptors and by Berger et al. (1989) for cardiac sympathetic receptors. That is, all displayed low-pass-filter characteristics with a corner frequency of about 0.02 Hz and a pure time delay. These findings again indicate that it is the end-organ response that is primarily responsible for the frequency characteristics of heart rate and that the high-frequency-filter characteristics of the sympathetic innervation preclude appreciable contributions to RSA at frequencies beyond 0.15 Hz.

The effects of pharmacologic blockade of muscarinic or adrenergic receptors are in general agreement with these interpretations. The literature is consistent in indicating that respiratory–frequency heart rate variability is mediated largely by changes of vagal cardiac nerve traffic. RSA is nearly abolished by cholinergic blockade or functional vagotomy but is not generally attenuated by beta-adrenergic blockade (Akselrod et al., 1981, 1985; Cacioppo et al., 1994; Coker, Koziell, Oliver, & Smith, 1984; Katona & Jih, 1975; Grossman, Stemmler, & Meinhardt, 1990; Japundzic, Grichois, Zitoun, Laude, & Elghozi, 1990; Kollai & Mizsei, 1990; McCabe, Youngue, Ackles, & Porges, 1985; Pagani et al., 1986; Pomeranz et al., 1985). Consistent with previous findings in dogs (Akselrod et al., 1981), for example, Pomeranz et al. (1985) reported that cardiac parasympathetic blockade in humans eliminated all heart rate fluctuations above 0.15 Hz and about 75% of those below 0.15 Hz, whereas sympathetic blockade had little effect on fluctuations above 0.15 Hz. These findings confirm the differential frequency response of the sinus node to parasympathetic and sympathetic modulation and reveal that high-frequency (HF) cardiac rhythms are mediated primarily by vagal innervation of the SA node. Because RSA arises from the respiratory inhibition of parasympathetic control, its magnitude may provide an indication, albeit imperfect, of basal levels of vagal cardiac nerve traffic (Eckberg et al., 1988; Grossman & Kollai, 1993; Kollai & Mizsei, 1990; Porges, 1986).

Heart Rate Variability at Low Frequencies

In accord with the temporal dynamics of the parasympathetic and sympathetic cardiac innervations as outlined earlier, both autonomic branches can influence lower frequency cardiac rhythms. Published literature on autonomic mediation of LF heart rate variability is controversial. Some workers, notably Malliani and associates (Malliani et al., 1991; Pagani et al., 1986), have argued that LF heart rate rhythms reflect mainly fluctuations of sympathetic traffic to the SA node. Other workers, who probably constitute a majority, have argued that LF rhythms reflect fluctuations of both autonomic branches. The Malliani group has further proposed that power in the LF and HF bands, especially when expressed in normalized units,[3] reflects the relative balance between sympathetic and vagal control and that this sympathovagal balance can be indexed by the LF/HF ratio (e.g., see Malliani et al., 1994; Montano et al., 1994). Others have argued that the LF/HF ratio cannot be considered as an index of sympathovagal balance (e.g., see Eckberg, in press).

Because neither vagal nor sympathetic nerve traffic to the human heart has been measured directly, conclusions regarding the mediation of LF heart rate fluctuations are based on indirect evidence. Sympathetic traffic to skeletal muscle (Saul, Rea, Eckberg, Berger, & Cohen, 1990) and the vasculature (Guzzetti et al., 1994; Koh et al., 1994) both fluctuate at low frequencies. In accord with the low-pass characteristics of sympathetic cardiac synapses, LF heart rate variability has been reported to be reduced by pharmacological blockade of cardiac sympathetic synapses (Akselrod et al., 1981; Murphy, Sloan, & Myers, 1991; Pomeranz et al., 1985) or stellectomy (Pagani et al., 1986). Consistent with these observations, numerous investigators have found that sympathetic activation and parasympathetic withdrawal, known to occur with maneuvers such

[3]The use of normalized units is intended to remove differences in overall variance across conditions. The equation for normalized units is $P_{nu} = 100 * P/(\sigma^2 - P_{VLF})$, where P_{nu} is the power of the component in normalized units (*nu*), P is the absolute power of the target LF or HF component (in ms^2), σ^2 represents the total power (in ms^2), and P_{VLF} is the power in the VLF component (in ms^2) extending down to DC.

as tilt, are reflected in a shift from higher to lower frequency heart rate fluctuations. Also consistent are reports that sympathetic activation triggered by vasodilators can lead to enhanced LF variability (Pagani et al., 1986), and another known sympathetic stimulus, myocardial infarction, has been found to cause a shift from HF to LF variability (Lombardi et al., 1987).

However, beta-adrenergic blockade may not always reduce appreciably LF cardiac rhythms and can even enhance them slightly (Cacioppo et al., 1994; Taylor, Carr, & Eckberg, 1997). Moreover, LF power is not invariably increased by vasodilators (Koh et al., 1994) and may be unaltered after blockade of sympathetic outflow by high spinal anesthesia (Hopf, Skychally, Heusch, & Peters, 1995). These findings suggest that sympathetic modulation may not be the sole determinant of LF R–R interval power. In addition, atropine has been consistently reported to reduce LF heart rate rhythms (Akselrod et al., 1981; Cacioppo et al., 1994; Koh et al., 1994; Murphy et al., 1991). To some extent, the relative contributions of sympathetic and parasympathetic control to LF heart rate variability is a function of posture because sympathetic tone is minimal while supine but is generally considerably higher while standing. Moreover, sympathetic and parasympathetic systems may interact in complex ways in the generation of LF heart rate rhythms. Because healthy humans operate along the relatively linear portion of the arterial pressure–vagal baroreflex function (Rea & Eckberg, 1987), changes in blood pressure trigger corresponding changes in vagal–cardiac nerve traffic. Thus, sympathetically mediated arterial pressure changes may translate into vagal–cardiac nerve responses, so that the latter may bear some quantitative relation to sympathetic traffic. In this regard, Pomeranz et al. (1985) reported that either cardiac parasympathetic or sympathetic blockade attenuate LF cardiac rhythms by about 75%. This result suggests a degree of interaction or nonlinear resonance at lower frequencies due to the combination of vagal and sympathetic modulation. This resonance may be explained in part by the fact that initially out-of-phase sympathetic and parasympathetic responses come into phase at around 0.1 Hz due to the delays inherent in the sympathetic response (Saul et al., 1991). Regardless of the specific mechanisms, it is clear that both sympathetic and parasympathetic systems can contribute substantially and in complex ways to LF cardiac rhythms.

Heart Rate Variability at Very Low Frequencies

The VLFs have been defined differently in the literature (see Footnote 2) but probably are characterized best as those below the range of the heart rate and blood pressure rhythms near 0.1 Hz. Bigger et al. (1992) defined a VLF range of 0.0033–0.04 Hz and a ULF range of less than 0.0033 Hz, although the boundary between these frequencies was based on pragmatic rather than on functional considerations. Others have considered the LF range to begin at about 0.07 Hz, with all lower frequencies considered to be VLF (Pagani et al., 1986). Additional confusion may arise from the term *Mayer wave*, which has been used variably to refer to only fluctuations at frequencies not exceeding 0.05 Hz (Madwed & Cohen, 1991; Preiss, Iscoe, & Polosa, 1975; Preiss & Polosa, 1974) or fluctuations including the *10-s rhythm* (0.1 Hz) as originally defined by Mayer (1877) in rabbits. For the purposes of this review, VLF variability is considered as fluctuations beginning at the 0.0033-Hz lower frequency limit as defined by Bigger et al. (1992) and including frequencies up to 0.05 Hz, a commonly used value for VLF oscillations in dogs (Madwed & Cohen, 1991; Madwed, Albrecht, Mark, & Cohen, 1989).

A review of the literature reveals a broad array of potential stimuli and conditions that may contribute to VLF rhythms. These stimuli and conditions include hemorrhage, aortic constriction, acidosis, alkalosis, vasoactive agents, high altitudes, asphyxia, and anesthesia in animals (Koepchen, 1984; Madwed, 1986; Madwed & Cohen, 1991) and posture, congestive heart failure, and slow variations in breathing patterns in humans (Cherniack & Longobardo, 1973; Goldberger, Findley, Blackburn, & Mandell, 1984; Novak, Novak, Kus, & Nadeau, 1995; Pomeranz et al., 1985; Saul, Arai, et al., 1988). In addition, nonrhythmic power in the VLF range is common and often dominates recordings of heart rate variability under spontaneous ambulatory conditions (Bigger et al., 1995). The explanations for VLF rhythms have been as diverse as the stimuli and include thermoregulatory processes (Kitney, 1975, 1980), the renin–angiotensin system (Akselrod et al., 1981; Bonaduce et al., 1994; Taylor et al., 1997), hemodynamic feedback delays (Di Rienzo, Castiglioni, Parati, Mancia, & Pedotti, 1996; Guyton & Harris, 1951; Madwed et al., 1989; Saul, Berger, Chen, & Cohen, 1989), mechanical and central neural effects of breathing patterns (Cherniack & Longobardo, 1973; Dykes et al., 1986; Preiss et al., 1975; Saul, Kaplan, & Kitney, 1988; Saul et al., 1989), a central oscillator (Preiss et al., 1975), spinal reflexes (Fernandez de Molina & Perl, 1965), and vascular autorhythmicity (Siegel, 1983). Regardless of their mechanisms, great interest in VLF and ULF rhythms relates to their almost ubiquitous presence, combined with the observations that slow rhythms especially in the ULF range are excellent predictors of cardiac death after myocardial infarction, independent of associated hemodynamic abnormalities (Bigger et al., 1992, 1996; Malik & Camm, 1990). Their etiology in specific clinical conditions remains an important area of research. In view of the limited understanding of these rhythms and their minimal applications in psychophysiological studies thus far, VLF and ULF rhythms will not be considered further.

Analytical Methods and Quantification

Historical Trends

Two related historical trends are apparent in the measurement and quantification of heart rate variability. Early methods, mostly used to assess fetal heart rate variability, were oriented to processing of short-term tachograms and involved simple numerical estimates such as the difference between the shortest and longest cardiac cycle (Parer & Parer, 1985). Newer distribution-based methods were developed on more solid mathematical foundations (Kleiger, Miller, Bigger, Moss, & Multicenter Post-Infarction Research Group, 1987). These approaches treat the population of R–R intervals or pairs of adjacent R–R intervals as if they were a set of temporally unordered data and express variability either by conventional statistical measures or by the geometric properties of histograms or other graphical representations (Malik, 1995).

In basic research studies, however, it became apparent that specific patterns of heart rate variability may be related to particular physiological processes and mechanisms. Modern analytical methods that treat the R–R interval data as a series were subsequently introduced to extract periodic components from the pattern of heart period fluctuations. These approaches not only afforded more complete and sophisticated representations of the data but also fostered further refinements of theoretical constructs. Chess, Tam, and Calaresu (1975) and Sayers (1973) introduced spectral analyses to the measurement of heart rate variability, and Porges and others introduced cross-spectral analysis as a method of evaluating the linkage between respiration and heart rate variability in humans (Porges et al., 1980; see also Bernardi, Rossi, & Ricordi, 1992). Porges et al. speculated that the sum of the spectral densities

in the heart rate spectrum associated with respiration may provide an estimate of vagal control of the heart, and Akselrod et al. (1981) proposed that the respiratory rhythm in the heart rate spectrum was related to vagal control, whereas two slower frequency bands were related to an interaction between vagal and sympathetic influences.

The history of psychophysiological research also reflects these trends. Early research focused on the use of descriptive statistics (e.g., Lacey & Lacey, 1958; Lang et al., 1967; Porges & Raskin, 1969), but by the late 1970s there was a growing awareness of more sophisticated methods of quantifying heart rate variability through time-series analyses. Time-series analyses offered a more powerful method for modeling periodic components of heart rate that might have physiological and psychophysiological significance. It became increasingly clear that the procedures selected to quantify this variability are critical both for extracting physiologically meaningful information and for developing models relating physiological activity to psychological processes and behavior.

Overview of Measures and Methods

There are two basic approaches to quantifying heart rate variability: (a) use of global descriptive statistics to characterize the distribution of heart periods (e.g., range, standard deviation, and variance) and (b) modeling of periodic patterns to extract specific frequency components of variance that relate to functional processes or physiological mechanisms (e.g., RSA). The global descriptive statistics generally consider the total population of R–R intervals (or differences between adjacent intervals) as isolated or independent data samples, whereas periodic patterns focus on the serial linkages among the data elements. These two approaches are not convergent with the distinction between time-domain and frequency-domain analyses. Time-domain methods can be used to model periodic processes, and any frequency-domain method can be transformed into the time-domain method if the data are stationary (Brillinger, 1975). Numerous summary measures of heart rate variability have been employed or proposed over the past several decades. Some of the more commonly employed methods are summarized here.

Descriptive statistical methods. A wide variety of estimates of heart rate variability have been employed, including conventional measures such as the standard deviation of heart periods within a recording epoch. Many of the common time-domain statistical measures have been summarized in the report of the Task Force (1996). The Task Force recommended four time-domain measures for general use in clinical studies: two that index overall heart rate variability, one that estimates short-term variability, and another that estimates long-term variability. The two measures recommended for overall variability estimates are: (a) the standard deviation of all normal heart periods (SDNN) and (b) the triangular index (Malik, 1995; Task Force, 1996). The triangular index measures the general dispersion of R–R intervals around the modal value, expressed as the ratio of the total number of normal R–R intervals to the number of R–R intervals within the modal bin of the R–R interval histogram. The recommended estimate of short-term variability is the root mean square of the successive beat differences and that for longer-term variability is the standard deviation of the mean R–R interval for each 5-min epoch of the recording. Although these simple time-domain measures are sensitive to the distribution characteristics of the data, they entail minimal quantitative assumptions. These measures may provide important summary statistics for long-term recordings or when ectopic beats preclude more sophisticated analyses. They have limited application in basic psychophysiological research, however, where a more precise parsing of the frequency components of heart rate variability is desired.

Peak-to-valley statistic. One commonly employed time-domain estimate of short-term variability does serve to parse respiratory frequency oscillations (RSA) selectively from other periodic components. In this method, RSA is quantified as a breath-by-breath, peak-to-valley measure of heart rate fluctuations (Katona & Jih, 1975; Hirsch & Bishop, 1981; Eckberg, 1983; Raczkowska, Eckberg, & Ebert, 1983). This statistic represents the difference between the longest and shortest heart period within the respiratory cycle. The peak-to-valley method was implemented by Grossman and Svebak (1987) and Grossman, van Beek, and Wientjes (1990) as the mean difference between the maximum heart period associated with inspiration and the minimum heart period associated with the expiration for each respiratory cycle in the record. Adjustments are made for respiratory cycles during which heart period does not covary with respiratory phase. This approach yields a simple range statistic that achieves respiratory-frequency selectivity by direct registration of heart rate changes to the ongoing respiratory rhythm.

Spectral analyses. Spectral methods produce a decomposition of total variation of a data series into its frequency components, which can be expressed in the form of a spectral density function that depicts spectral power as a function of frequency. Spectral power for a given frequency band can then be quantified by deriving the area under the spectral density function within the specified frequency range. Kay and Marple (1981) provided an extensive overview of many of the techniques available for spectral analysis (see also Chatfield, 1989). The two most common approaches to spectral analysis of heart rate variability are the fast Fourier transform (FFT) technique (e.g., Akselrod et al., 1981; Berger, Akselrod, Gordon, & Cohen, 1986) and autoregressive (AR) modeling (Pagani et al., 1986). The main difference between the FFT and AR approaches is the way in which the data are viewed. The FFT analysis assumes that the time series contains only deterministic components, whereas the AR analysis treats data as a composite of deterministic and stochastic components. The spectrum computed with the FFT is derived from all the data regardless of how well they fit a model based on peaks in the spectral distribution. With AR techniques, the time-domain data are used to identify a best-fit model from which a number of peaks and the final spectrum are derived. AR techniques concentrate on the more significant peaks, attempting to exclude "noise," whereas FFT-based techniques include all data. Thus, in its worst basic application the FFT approach could be considered a descriptive method and the AR approach would be more consistent with a stochastic or statistical approach. In practice, this distinction is blurred by the common application of smoothing algorithms or windowing to stabilize variance estimates from FFT analyses. Although there are a number of advantages and disadvantages to each of these methods, there are also many similarities that in practice usually lead to essentially equivalent results (e.g., see Figure 3 in Parati, Saul, Di Rienzo, & Mancia, 1995).[4]

[4]Regardless of the spectral technique used, it is important that spectra be computed as spectral density (*y*-axis in units of ms^2/Hz or bpm^2/Hz) so that the spectral amplitude is not dependent on the record length and integration of the spectral area produces variance (ms^2 or bpm^2). A quick check to confirm that the correct units are being used is Parseval's theorem, which states that integration of the entire power spectrum should be equal to the total variance of the data, when trends are dealt with similarly for both the frequency- and time-domain computations.

Moving polynomial method. An additional approach that has been employed frequently in the literature is the proprietary moving polynomial method of Porges (Porges, 1986; Porges & Bohrer, 1990). This approach is basically a time-domain method but, like spectral techniques, allows derivation of components of heart rate variability within specified frequency bands. Briefly, this method first derives a heart period time series and then applies a moving polynomial filter to remove slow trends in the data. A specified bandpass filter is then applied to the data to remove variance outside the target frequency band. The statistical variance of the residual data is derived as an estimate of heart rate variability within the target frequency band.

Additional measures of heart rate variability. Other methods to describe heart rate variability have been employed in the literature. The quantification of RSA can be viewed as a spectral analysis problem associated with a bivariate time series consisting of heart period data and an appropriate measure of respiratory activity. Porges et al. (1980) introduced cross-spectral analysis as a method for evaluating the coupling between respiration and heart rate variability in humans (see also Bernardi et al., 1992). Berger et al. (1989) and Saul et al. (1991) employed transfer function analysis to quantify respiratory influences on heart rate variability. This approach determines the frequency-dependent transfer of respiratory modulations to heart rate rhythms, with the magnitude and phase angle associated with the transfer function providing insights into the dynamics of respiratory–cardiac coupling. This represents a potentially powerful research approach but requires broadband spectral power in the respiratory signal, which is not generally feasible in psychophysiological studies.

A recent approach to the study of heart rate variability considers the beat of the heart to reflect the operations of nonlinear dynamic systems. The Poincaré plot is a graphical approach that plots the value of a given heart period (on the abscissa) against the subsequent heart period (on the ordinate), with the overall shape of the distribution then used to characterize the dynamics of the system. Unfortunately, the standard construction of a Poincaré plot does not reflect the number of samples at each point of the graph, so that virtually identical plots could be constructed from R–R interval sequences having remarkably different patterns of variability. Consequently, the visual judgment of the shape of a Poincaré plot can be misleading (Hnatkova, Copie, Staunton, & Malik, 1995). The Poincaré plot, however, is only a limited tool of the broader approach derived from chaos theory, which treats data as reflecting the operations of a deterministic system. In these approaches, R–R intervals are assumed to be related through a complex nonlinear relationship. Although chaos theory and estimation of the associated fractal dimension has been explored in the literature (Glass & Mackey, 1988; Goldberger, 1992; Peng et al., 1995), implications of the work for understanding the mechanisms of heart rate variability and autonomic control have yet to be fully clarified (e.g., Kanters, Holstein-Rathlou, & Agner, 1994; Kanters, Hojgaard, Agner, & Holstein-Rathlou, 1996). This remains a promising approach, but its ultimate utility in understanding cardiac control and heart rate variability will depend on further development.

Guidelines, Recommendations, and Caveats

The following discussion highlights important issues and considerations in the analysis and interpretation of heart rate variability and offers suggestions and recommendations intended to promote standardization and comparability across studies and disciplines. These suggestions and recommendations should be viewed as general guidelines to foster research in a complex area rather than as rigid rules that might impede novel research efforts or methodological developments. The discussion is not a comprehensive consideration of methodological issues in this area but focuses on selected issues and particular problem areas of relevance to psychophysiological research. Additional discussion of methodology can be found in Brockwell and Davis (1991), Chatfield (1989), Grossman (1992b), Kay and Marple (1981), Mulder (1992), and Porges and Byrne (1992).

Signal Acquisition and Preliminary Processing

Meaningful analysis of heart rate variability is dependent on the integrity of the basic cardiac signal input, generally in the form of the electrocardiogram (ECG). Details of recording equipment and procedures are discussed elsewhere (Jennings et al., 1981; Pipberger et al., 1975; Sheffield et al., 1985). With modern methods, the ECG signal is generally digitized by computer, and a series of R–R intervals is then derived either on- or off-line. Although it may not always be feasible, the raw ECG record ideally would be preserved to permit evaluation of the integrity of the recorded signal, to identify abnormal beats and for artifact editing.

An important consideration arises as to the accuracy of R-wave timing because this timing defines the basic resolution of subsequent analyses. The digitization rate sets a limit on this resolution because it defines the minimal amplitude of an oscillation (in milliseconds) that can be detected. Because experimental effects for some subjects or conditions may represent only small variations in the amplitude of cardiac rhythms, an optimal and generally applicable digitization rate would be 500–1000 Hz (Merri, Arden, Motley, & Titlebaum, 1990; Riniolo & Porges, 1997). This rate would provide a basic resolution of 1–2 ms, which may be necessary to resolve very-low-amplitude heart period fluctuations as seen, for example, in premature infants, rats, or denervated hearts of transplant patients (e.g., see Riniolo & Porges, 1997). Quantitative examinations of this issue by Merri et al. (1990) and Riniolo and Porges (1997), however, indicate that a resolution of 4 ms (250-Hz digitization rate) may be adequate for typical levels of RSA in normal human adults. This is the lowest sampling rate that can be recommended for most psychophysiological studies. Although the 128-Hz digitization rate provided by some versions of the Holter monitor is not optimal, it may be useable for some studies with large-amplitude rhythms in normal adults (Riniolo & Porges, 1997). In view of the inherent error in R-waving timing, some type of template matching or interpolation algorithm should be used, especially with digitization rates below 250 Hz, to improve the temporal accuracy of R-wave peak identification (Bartoli, Baselli & Cerutti, 1982; Friesen et al., 1990). Digitization rates below 100 Hz are not acceptable because they provide insufficient sampling of the QRS complex.

In addition to the basic limits of resolution afforded by the digitization rate, errors in R-wave timing can be introduced by noise in the ECG signal. Noise can lead to the spurious identification of the R-wave due to variations in peak amplitude, or may result in the voltage of an off-peak sample being higher than one at the peak of the R-wave. Consequently, simple maxima-based peak-finding algorithms applied to raw digitized records are not optimal. There are many approaches to this problem, ranging from simple smoothing or filtering of the digitized data to more sophisticated algorithms that use the derivative or template matching to improve the accuracy of R-wave timing (Friesen et al., 1990). One commonly employed approach entails a parabolic interpolation of the sample points around the R-wave (Bartoli et al., 1982; Merri

et al., 1990). Parabolic interpolation reduces the effects of extraneous noise on R-wave timing and appropriately interpolates between adjacent sample points. This or other appropriate method is highly recommended in deriving R–R intervals, especially from recordings acquired at lower sample rates. Such approaches can reduce, but do not completely eliminate, the effects of noise on R–R interval timing. Consequently, it is always important to minimize noise by rigorous recording methods.

In some cases, R–R intervals may be derived from analog systems (such as Schmitt triggers, window discriminators, or slope detectors) rather than from digitized records. In this case, digitization rate is not a factor, but noise and other errors of R-wave timing can similarly limit the accuracy of R–R interval estimation. A variety of other sources of error may also be inherent in recording systems. If the ECG is recorded on FM tape for off-line processing, for example, the basic fidelity of the recording system and errors introduced by stretch of the magnetic media will limit resolution further. Regardless of the nature of the hardware, it is highly recommended that the accuracy of any recording system be evaluated on a regular basis by the use of simulated calibration signals with known characteristics (for guidelines, see Task Force, 1996).

A heart period series could also be derived from biological signals other than the ECG, such as photoplethysmographic records or continuous blood pressure recordings. Accurate fiducial point identification can be especially problematic with these signals because they often lack sharp peaks. When these signals are derived from distal sources, such as the arm or finger, the timing of pressure or photo-optical signals and the precise shape of the waveform may be influenced by factors such as stroke volume and vascular tone. A template-matching approach to peak identification is particularly important with such signals (Daffonchio et al., 1995). Although the ECG signal is greatly preferred for research purposes, direct comparison between ECG and blood pressure pulse intervals derived from a femoral artery catheter in the rat has revealed virtually identical R–R interval means and standard deviations (Daffonchio et al., 1995). Similarly, spectral analyses based on the ECG and pulse intervals derived from the radial artery in humans were also comparable, although some modest deviations were apparent (Parati et al., 1990). Given available information, the use of intra-arterial pressure pulses and a sophisticated peak detection algorithm may be acceptable, at least for moderate to high levels of heart rate variability. More indirect measures, such as photoplethysmographic signals or Finapres-type measures, require further validation.

The use of analog cardiotachometers to derive an R–R interval series is not recommended. These devices provide on-line transformation of R–R intervals into DC output levels and have been used to monitor heart rate in psychophysiological studies. The R–R interval to DC level transformations must ultimately be retransformed into the R–R interval series required for heart rate variability analyses. Each of these transform steps is associated with both random errors and nonlinearities, which add to the overall error variance and may mask experimental effects. This approach may be adequate for measures of basal chronotropic state and reactive response but is generally not appropriate for studies of heart rate variability. Although modern digital cardiotachometers are far more accurate and linear than older devices, all suffer from a second major disadvantage. The DC output of a cardiotachometer at any time is related to the prior heart period, but the duration of that output is a function of the current beat (de Boer et al., 1985; Thorne, Engel, & Holmblad, 1976). This inherent dissociation between the R–R interval and real time adds considerable complexity in maintaining temporal registration of the R–R series with other events or signals. Although an adequately calibrated cardiotachometer with appropriate resolution may be usable for analysis of heart rate variability, it is generally easier and more accurate simply to time the R-wave-detector output that is typically provided by these devices.

Artifact processing. With the possible exception of anesthetized or immobilized subjects, artifacts from a variety of sources are likely to contaminate the ECG signal. Adequate resolution of these artifacts is important because they can substantially bias results (Berntson & Stowell, in press; Malik et al., 1993; Ramanathan & Myers, 1995; Xia, Odemuyiwa, Gill, Malik, & Camm, 1993). Unfortunately, artifact-laden epochs within an R–R series cannot simply be deleted because this would disturb the continuity of the series that is necessary for analysis of rhythmical variations. Artifacts (either missed R-waves or spurious detections) produce large deviations in estimated R–R intervals that usually can be identified visually in graphical displays of the R–R interval series. This method is tedious, especially with large numbers of participants or long-term recordings and requires subjective judgments that may be difficult in records with a high basal level of variability. Therefore, it is generally preferable to use a distribution-based artifact-detection algorithm with known performance characteristics (e.g., Cheung, 1981; Berntson, Quigley, Jang, & Boysen, 1990; Linden & Estrin, 1988). A combination of both automated and visual approaches is optimal because automatically detected outliers need to be classified as artifacts or abnormal beats and handled accordingly.

For artifacts arising from a spurious R-wave detection, no information is lost in the R–R series, and the actual heart period can be restored precisely by simply summing the two (or more) spuriously short periods that constitute the actual heart period. Review of the ECG record may be useful in this process and is valuable for differentiating an artifact from an ectopic or abnormal sinus beat. Because an abnormal beat may reset or otherwise alter the ongoing cardiac rhythm, it may not be possible for the R–R series to be simply "corrected." The issue of abnormal beats will be considered below.

In contrast to spurious R-wave detections, information is lost if an R-wave goes undetected. In such cases, the location of the missed beat within the spuriously long R–R interval is unknown and cannot be derived precisely from the R–R interval series. There are several approaches to the resolution of missed beats. In order of preference, these are (a) measuring the actual R–R intervals, if identifiable, from the ECG record; (b) interpolating the missing R-waves from surrounding beats; and (c) splitting the spuriously long beat into two (or more) equivalent R–R intervals. None of these approaches would bias estimates of the overall mean of the heart period series, although they may have some effect on the variance. As long as the incidence of missed R-waves is small, such approaches would be expected to introduce minimal distortion in estimates of heart rate variability, although validation studies are needed to formulate specific guidelines. Far more serious are biases associated with unresolved artifacts because a single missed R-wave within a 2-min recording epoch can increase estimates of heart rate variability severalfold (Berntson & Stowell, in press).

An alternative approach to resolving artifacts is to correct the time series rather than the R–R series by interpolation (Saul, Arai et al., 1988). In this approach, deviations from the typical (criterion) statistics of the time series are identified as undesirable for

spectral analysis because of the gross broadening of spectral power they produce. The LF information is preserved without adding spurious power but at the cost of some reduction in HF information (Albrecht, Cohen, & Mark, 1988). This method treats abnormal beats as artifacts, however, and may not be appropriate for individuals with low-amplitude variability, where small deviations can account for a large percentage of the variance. However, this approach would be expected to produce minimal distortion in normal individuals with few abnormal beats.

Abnormal beats. Artifact detection and processing of abnormal beats are more problematic in individuals with cardiac arrhythmias. The value of heart rate variability in psychophysiological studies is related to the fact that the sinus rhythm is under predominant autonomic control, and periodicities in this control may offer insights into physiological mechanisms and psychophysiological relationships. Cardiac arrhythmias, however, may arise from abnormalities in the sinus rhythm generator or may reflect ectopic sources that can override, bypass, or even reset the normal sinus rhythm. Although these arrhythmias may be modulated by autonomic outflow, the relationships between autonomic control and the occurrence and timing of arrhythmic beats have not been well characterized. Moreover, abnormal rhythms can distort the distribution characteristics of the R–R intervals and seriously violate the assumptions underlying many analytical methods. Consequently, it may be difficult to interpret heart rate variability in the presence of abnormal rhythms. Although the pattern of heart rate variability may be useful to characterize the nature of the arrhythmia or to predict clinical outcomes, arrhythmias can compromise inferences concerning autonomic control. Moreover, the frequency of abnormal beats may be altered by experimental manipulations such as stress, thus confounding experimental comparisons.

If interest is in the normal rhythm of the heart, interpolation could be used to replace occasional abnormal beats or to correct the time series (Saul, Arai et al., 1988). Alternatively, analyses could be limited to data segments that are free of anomalies, but that can lead to selection bias, and the problem would be exaggerated with increasing numbers of abnormal beats. This problem should be acknowledged explicitly, and some indication of the extent of data selection should be given. Application of both of these approaches may be desirable, if abnormal beats are more frequent, because concordance between results from segments of normal R–R intervals and from interpolated data would raise confidence in the outcome. In any event, the specific procedures should be clearly described, and their potential contributions to the results discussed. For recordings with a high rate of abnormal beats, analyses probably should be limited to time domain statistics (see Selection of Appropriate Analytical Methods).

Heart period versus heart rate. Both heart rate and heart period have been employed as basic metrics in studies of cardiac rhythms. Heart period is more typically employed and is generally preferred, especially when the interest is in indexing parasympathetic control (Eckberg & Sleight, 1992; Faes, De Neeling, Kingma, TenVoorde, & Karemaker, 1995). Heart rate is a nonlinear transformation of the basic R–R interval measure and transforms require an explicit rationale. A consistent finding in the literature is that the function relating the frequency of vagal activation to heart rate is hyperbolic, whereas that for heart period is relatively linear, at least over typical operating ranges (Dexter, Levy, & Rudy, 1989; Parker et al., 1984; Rosenblueth & Simeone, 1934; for reviews, see Berntson et al., 1995; Eckberg & Sleight, 1992). The approximate linearity with heart period confers a considerable advantage on this metric because the derived amplitude of RSA or other parasympathetic-based rhythms should be independent of basal chronotropic state—a relationship that does not hold for heart rate.[5] The issue is somewhat more complex for sympathetic contributions to lower frequency rhythms because functions relating the frequency of sympathetic neural activity are nonlinear for both heart rate and heart period. Over much of its operating range, however, the sympathetic function also is reasonably linear when expressed in heart period (see Berntson et al., 1995; Eckberg & Sleight, 1992). Moreover, the dynamic range of parasympathetic control is considerably greater than that of the sympathetic branch, and variations in basal vagal control also can introduce baseline dependencies in sympathetic estimates when the chronotropic state is expressed in heart rate (Berntson et al., 1995). This baseline dependency can appear as an interaction between sympathetic and vagal controls of the heart (see Quigley & Berntson, 1996) and can complicate interpretation of heart rate variability.

Although heart period has advantages for analysis of cardiac rhythms, heart rate has often been employed, and analyses based on heart period and heart rate may produce generally similar patterns of results (for exceptions, see Faes et al., 1995; Janssen, Swenne, de Bie, Rompelman, & van Bemmel, 1993). To maintain comparability with previous studies or for other pragmatic reasons, heart rate also may be useable. To avoid loss of HF resolution, heart rate should be derived on a beat-by-beat basis and a time series should be derived.

These considerations raise an issue as to the appropriate use of the phrases *heart rate variability* and *heart period variability*. *Heart rate variability* has been used as a general descriptor in the literature for measures derived from either heart rate or heart period data. By this convention, *heart rate variability* may be used regardless of the specific metric by which the data are expressed. It is recommended, however, that *heart period variability* be used as a descriptor only when the analyses are based on R–R interval data.

Derivation of a data series. Successive R–R intervals entail a series of data points spaced unevenly in time, whereas time-series analyses assume the data are sampled at equal time intervals. Spectral analysis of R–R series (or beat-by-beat heart rate series) can be analyzed by spectral methods because the data points are equidistantly spaced in the beat series (de Boer, Karemaker, & Strackee, 1985; Rompelman, Snijders, & van Spronsen, 1982). The direct submission of an R–R series to spectral analyses is not optimal for most purposes, however, because the abscissa of the spectral plot is expressed in units of cycles/beat rather than of cycles/second. A problem with this approach is that beats vary in duration, and the results may not be related easily to events or processes (such as respiration) in the time domain (Berger et al., 1986; de Boer et al., 1985). The dimension of cycles/beat can be translated roughly to

[5]Different versions of the integral pulse frequency modulation (IPFM) model have been suggested to be more compatible with either heart rate or heart period as the preferred metric (e.g., see Berger, Akselrod, Gordon, & Cohen, 1986; de Boer, Karemaker, & Strackee, 1984; Janssen et al., 1993; Rompelman, Coenen, & Kitney, 1977). The IPFM model, however, does not consider all determinants of chronotropic state and remains limited (e.g., see Janssen et al., 1993). Recent studies have clarified considerably the cellular dynamics of synaptic processes at the sinoatrial node. The model of Dexter, Levy, and Rudy (1989), based on these studies, is in accord with the uniform finding of a linearity between vagal frequency and heart period (for review, see Berntson, Cacioppo, & Quigley, 1995).

the time dimension by multiplying by the mean heart period, and as long as heart periods do not vary appreciably, time series and R–R series produce generally comparable results (Baselli et al., 1987). The translation is not precise and becomes less accurate as heart period varies (Berger et al., 1986) because beats differ in duration, and for analyses of R–R series, beats are not appropriately weighted by the time they occupy.[6] A related problem is that analyses of a fixed number of beats across experimental conditions would be based on differing time epochs if basal heart periods differed, which is potentially problematic because heart period variability tends to increase over time. This problem is exacerbated by laboratory stressors or other manipulations that may lead to sizeable differences in basal heart periods across experimental groups or conditions. In view of these considerations, the use of equal interval time-based data is preferred for spectral analyses unless the interpretation does not entail relations to the time domain or adequate justification is provided for the use of an R–R series.

A variety of methods have been used to derive a time series (de Boer, Karemaker, & Strackee, 1984; de Boer et al., 1985; Janssen et al., 1993; van Steenis, Tulen, & Mulder, 1994). One approach is to sample, at fixed time intervals, the value of the current heart period at each sample point. This approach assigns an identical value to data points falling within a given beat and results in sharp transitions for samples that fall just before and just after the occurrence of an R-wave, which can lead to spurious noise in frequency-domain analyses. Consequently, it is preferable to use a sampling approach in which the value at a given point represents a weighted average of the beats that fall within the sample interval (e.g., see Berger et al., 1986; Berntson et al., 1995).

An important consideration in generating a time series is the selection of the optimal sample interval. By definition, an R–R interval represents a single sample per beat and has a maximum frequency content of half the sampling frequency, or 0.5 cycles/beat. For an average heart rate of 60 bpm (1 Hz), the maximum frequency content is 0.5 Hz. To avoid aliasing, the required sampling rate must be at least twice the lowest resolvable frequency (i.e., 1 Hz), and a sampling rate of 4 times the target frequency is more appropriate. For 0.5-Hz information, therefore, a sampling frequency of at least 2.0 Hz (500-ms sample interval) should be used. For children or other individuals with high heart rates, 4.0 Hz may be more prudent. Oversampling is inefficient, and although it may create the illusion of greater temporal resolution, it does not enhance the basic resolution afforded by the timing of the actual heart periods and the duration of the recording. For humans, a sample rate of 4 Hz would be applicable generally and would be sufficient to capture HF rhythms even at the high respiratory rates of infants and of adults during exercise.

[6]Graham (1978) offered an example of a 60-mile trip between two points (A and B) at 60 mph and a return trip at 30 mph. Graham posed the question of the average speed over the combined trips. The answer of 45 mph may seem intuitive, but it is incorrect. Although 45 mph represents the arithmetic mean of the speed across the two trips (i.e., speed/trip), the trips differ in duration and are not appropriately scaled by time. Because the outbound trip takes 1 hr and the return trip 2 hr, the average speed over both trips is 40 mph (1 hr at 60 mph, and 2 hr at 30 mph = [60 + 30 + 30]/3 = 40). Because the 45-mph estimate does not appropriately weight the two trips for their duration, it is a biased estimate of the average speed. If the speed were estimated to be 45 mph, for example, and the overall outbound and return trips took 3 hr, the estimated distance traveled would be 135 miles (45 mph × 3 hr), and the estimated distance between points A and B would be 67.5 miles. In fact, the distance between A and B is only 60 miles, and the overall trip is 120 miles.

The Issue of Stationarity

Spectral analysis inherently assumes that the data series is at least weakly stationary. Strict stationarity requires that the distributional characteristics of a series (including all moments) be invariant over time, whereas weak stationarity requires only that the first and second moments (mean and covariance) are stable across time. Stationarity is an important consideration because the presence of slow or irregular trends in the series can potentially distort analyses and lead to misinterpretations. This concern is not limited to frequency-domain analyses. Any estimates that attempt to extract and characterize specific periodicities over time may be distorted by slow linear or complex trends (Weber, Molenaar, & van der Molen, 1992a). This is a difficult issue because violations of stationarity in actual heart period data may be quite common (Grossman, 1992a, 1992b; Porges & Bohrer, 1990; Weber et al., 1992a).

The initial approach to this problem should always be to minimize nonstationarities by maintaining testing and subject conditions as stable as possible throughout the recording period. Moreover, because the probability of nonstationarities increases with the length of the sample epoch, it is generally advisable to avoid test epochs much beyond those necessary to extract the periodicities of interest. The ultimate goal is to avoid changes in context or subject state so as to minimize associated time-varying changes in the pattern of autonomic modulation of the heart, which is the dimension to be indexed by heart rate variability measures. In this regard, repetitive or time-varying experimental stimuli or events (e.g., task responses) may evoke phasic heart rate changes that could confound measures of heart rate variability. This is especially problematic if the event repetition rate falls within the frequency band of the cardiac rhythm of interest. Consequently, if a paradigm entails repeated experimental events, the repetition rate should be well outside the frequency band of interest for heart rate variability measures. Even so, caution needs to be exercised because stimulus- or response-driven cardiac reactions are rarely sinusoidal and may introduce broadband spectral noise or harmonics that lie well outside the basic event repetition rate. Irregularly presented stimuli could be used to minimize the rhythmical driving of heart rate but would not eliminate the problem of broadband noise and harmonic leakage and may lead to violations of stationarity. Consequently, transient experimental stimuli or events that evoke sizeable phasic heart rate responses probably should be avoided during recordings from which estimates of heart rate variability are to be derived unless specific methods are implemented to evaluate the potential impact on estimates of heart rate variability. Even stimuli that do not evoke sizeable cardiac responses should be employed only as necessary and then presented on an irregular basis or at a repetition rate that does not overlap the frequency bands employed for heart rate variability measures.

Despite reasonable precautions, nonstationarities may emerge in heart period data. Weber and colleagues suggested that local epochs of heart period data should be explicitly tested for nonstationarities and that only stationary segments should be selected for analysis (Weber et al., 1992a; Weber, Molenaar, & van der Molen, 1992b). A concern with this approach is that the prevalence of nonstationary segments may result in highly selected samples, which may not be representative of the data as a whole (Grossman, 1992a, 1992b). Other methods seek to remove slow nonstationary trends prior to analysis, based on linear or polynomial models (e.g., Litvack, Oberlander, Corney, & Saul, 1995; Porges & Bohrer, 1990). The application of bandpass filters to isolate the periodicities of interest may minimize the effects of

nonstationarities further (e.g., Litvack et al., 1995; Porges, 1986; Porges & Bohrer, 1990).

These approaches can improve the accuracy of estimate of a constant periodicity that is superimposed on slower trends in the data. Biological rhythms (such as RSA), however, often vary over time. This variation would violate assumptions of stationarity, not because the target rhythms are superimposed on lower frequency trends (i.e., changing mean levels) but because of inherent changes over time in the amplitude of variability (i.e., changing variance). In other words, the target signal itself might be nonstationary (Weber et al., 1992a). Because it may be an inherent dynamic feature of the signal, this nonstationarity cannot simply be removed or extracted. Indeed, alterations in RSA over time may be of primary interest in some psychophysiological studies. One approach to this problem is to analyze multiple short epochs within which stationarity is satisfied and to examine the dynamics of the signal by comparing results over time (e.g., Barbieri et al., 1996; Porges, 1986; Porges & Bohrer, 1990). In addition, Kitney and Darvish (1995) described several methods that are explicitly designed to characterize nonstationary signals and their dynamic changes, including modified Wigner distributions, moving periodograms, wavelet transforms, and short-term FFTs. Although these methods have not been widely employed in the literature on heart rate variability, they clearly warrant further consideration.

In summary, nonstationarities in heart period data may be common and can bias estimates of heart rate variability. Of special concern are experimental comparisons in which nonstationarities are more prevalent in one condition than in another because this difference would confound the results. Under many circumstances, however, moderate violations of stationarity may not seriously affect RSA measures (Grossman, 1992a, 1992b). Clearly, more research is necessary to clarify the consequences of violations of stationarity and the determinants of the magnitude of resulting biases. In the meantime, the issue of stationarity cannot be ignored. Prudent steps could include (a) minimizing nonstationarities in data, (b) removing slow trends by filtering procedures, (c) avoiding excessively long analytical epochs, (d) testing for the presence of nonstationarities (Weber et al., 1992a, 1992b),[7] (e) omitting highly nonstationarity segments in the data, and/or (f) applying analytical techniques explicitly designed to evaluate nonstationary signals

Selection of Appropriate Analytical Epochs

Standardization of recording lengths is important for comparisons among studies and is essential for within-study experimental contrasts. Heart rate variability tends to increase with the length of the analyzed record (Saul, Albrecht, Berger, & Cohen, 1988), so total variance (and to some extent that of its spectral components) is not a well-defined measure in the absence of information on the duration of the recording. The duration of the ECG recording should not be prolonged artificially because this increases the likelihood that assumptions of stationarity will be violated. However, biological rhythms are generally variable from cycle to cycle, and recordings should be sufficiently long to sample across these short-term variations. A recording duration of at least 10 times the wavelength of the lower frequency bound of the investigated component has been recommended (Task Force, 1996). Based on this guideline, a recording of approximately 1 min is needed to assess the HF component of heart rate variability, and approximately 2 min are needed to address the LF component. For clinical studies of HF and LF variability, standard recording periods of 5 min of a stationary system have been recommended (Task Force, 1996).

In many psychophysiological studies, it may not be possible to maintain a stable psychological or cognitive state over a 5-min period. In the interest of developing flexible standards that are broadly applicable among disciplines and over baseline and challenge conditions, the following guidelines are offered as an expansion of the Task Force (1996) recommendations. In accord with the basic Task Force guideline of at least 10 cycles of the target rhythm, standard recording periods of 1 min are recommended for HF variability and 2 min for LF (or LF and HF) variability.[8] When replicate samples are desired, they could be obtained over successive minutes or over discrete trials separated in time. In either case, analyses of multiple, short recording epochs (1–2 min) would minimize the likelihood of nonstationarities and permit evaluation of trial-to-trial variance and potential systematic changes over trials. In the absence of systematic change, the aggregate results of this approach should be comparable to analyses over longer (e.g., 5 min) epochs.

The criterion of approximately 10 cycles per analytical epoch also represents a reasonable standard for lower frequency rhythms. Based on this criterion, measurement of the lowest VLF frequencies (0.0033 Hz) would require about 50 min of recording. Because nonstationarity of the data becomes more likely and spectral components of heart rate variability become less well defined over time, analysis of ambulatory data and other long-term recordings is particularly problematic. One approach is to analyze 1- or 2-min segments at strategic points in the data set. An alternative is to limit analyses to time-domain descriptive statistics.

Selection of Analytical Method

Simple descriptive statistics provide only global estimates of heart rate variability or achieve at best crude frequency differentiation. Although these methods may have utility in clinical studies, they have minimal application in psychophysiological research, where a more precise parsing of frequency components is desired. There are a number of methods available to extract specific periodic components of heart rate variability. Each of these approaches has advantages and disadvantages, and no general consensus has emerged as to a single optimal approach. This discussion is limited to several of the more commonly employed methods.

Of the spectral methods, the FFT and AR modeling are most frequently employed. The spectrum computed with the FFT represents all the data in the analyzed series. In contrast, AR methods employ a model-fitting approach, from which a number of more significant peaks and the final spectrum are derived. When there is no a priori reason to believe that the data are generated from a system that produces fixed-rate oscillations or the oscillatory frequency is expected to vary with time, the FFT approach may be optimal. Alternatively, when a rhythm is expected at a discrete frequency, such as 0.1 Hz, or when the number of data points is low, the frequency resolution provided by an AR technique may be

[7]Brockwell and Davis (1991) described methods for testing stationarity. Tests are also available in some statistical packages, such as SAS and S-Plus. The method of Weber, Molenaar, and van der Molen (1992a) is tailored to heart rate data and is available gratis from M. W. van der Molen.

[8]These periods could be extended to 64 s and 128 s, respectively, for FFT analyses that require 2^N data points. It is possible to analyze even shorter periods and aggregate results over multiple analyses. In keeping with the present recommendation, however, the aggregate estimate should be composed of at least 10 cycles.

preferred. It is important to recognize, however, that AR results for a particular frequency band may differ dramatically, depending on the choice of the order for the AR model (Kashyap, 1980). This is an important issue because the specific implementation of an AR technique is likely to influence the results. Therefore, methodological consistency is important for comparisons among different studies, conditions, and individuals.

Practical considerations also may influence the selection of methods. The FFT requires 2^N data points, for example, which sets constraints on the duration and sampling rate of the recording to be analyzed. The moving polynomial method requires data points before and after the analytical epoch to "prime" the polynomial filter, and the peak-to-valley statistic is limited to RSA. These and other pragmatic issues may be important considerations in the selection of an appropriate analytical method.

Methods that extract periodic components of variance over time require that the data be at least weakly stationary and may produce biased results if this assumption is not met (Weber et al., 1992a). When the data satisfy stationarity assumptions and variance components are regular and sinusoidal, each of these approaches can yield essentially equivalent results. Moreover, the total spectral power derived by FFT and the sum of the band variances derived by the moving polynomial method will equal the total statistical variance of the data sample (minus the variance that is removed by trend removal and filtering). This result is also true of the AR approach if a sufficiently high-order model is employed. Although there are fundamental differences in the conceptual strategies underlying these quantitative modeling approaches, each can provide viable estimates of periodic components of heart rate variability when the data are reasonably stationary and the target rhythms are of moderate to high amplitude.

When applied to actual heart period data, however, some differences among the results of these alternative approaches may emerge. These differences are due in part to the fact that heart rate rhythms are rarely sinusoidal and often nonstationary (Weber et al., 1992a). Detrending methods can effectively remove some slow nonstationarity trends prior to analysis. Trend removal is inherent in the moving polynomial method, but it also has been employed prior to spectral analysis, although a simple linear model has typically has been used in this case (e.g., Litvack et al., 1995). In fact, removal of more complex trends (quadratic, cubic, adaptive filtering, moving polynomial filter) could be employed prior to any analysis. This approach warrants further study and development because the selection of an optimal filter model may increase the accuracy of heart rate variability estimates and diminish differences among the methods. Other differences can arise from the manner in which the results are expressed. Because the distributional characteristics of heart rate variability estimates may not meet the assumptions of parametric analyses, a natural log transformation of variance estimates has been suggested and is incorporated into the moving polynomial method (Porges & Bohrer, 1990; Riniolo & Porges, 1997).

When applied under comparable conditions (trend removal, bandpass filtering, natural log transformations, and aggregation across short analytical epochs), virtually identical estimates of RSA were obtained with FFT analyses and the moving polynomial method for both actual and simulated data (Litvack et al., 1995). Moreover, similar results have been reported with the moving polynomial method, FFT analysis, and the peak-to-valley statistic (Fahrenberg & Foerster, 1991; Grossman et al., 1990). A remaining issue is how well different methods fare under unfavorable conditions, such as when the amplitude of variability is very low or the data are nonstationary. This is an area that clearly warrants additional study.

In summary, there are substantial differences in the various methods used for deriving estimates of heart rate variability and in the assumptions and requirements of these methods. The relative advantages and limitations of alternative methods and comparisons between approaches have been considered (e.g., Byrne & Porges, 1993; Fahrenberg & Foerster, 1991; Grossman et al., 1990; Litvack et al., 1995; Parati et al., 1995; Porges & Bohrer, 1990; van Steenis et al., 1994). No consensus has emerged, however, on a single optimal approach.

Deriving Inferences From Heart Rate Variability

Gold Standards and Criterion Measures

Current scientific interest in heart rate variability emphasizes the potential relation of variance components to functional dimensions that presently cannot be measured directly. Given the broad claims concerning what heart rate variability measures represent, it is essential to identify reference criteria against which these measures may be validated. The relevant functional dimension may vary from discipline to discipline. In clinical cardiology, reference criteria have included cardiovascular morbidity and mortality (Bigger, Rolnitzky, Steinman, & Fleiss, 1994) and risk stratification for sudden cardiac death (Odemuyiwa et al., 1991). In cognitive psychophysiology, heart rate variability measures have been proposed as markers of mental effort, workload, and attentional development (Mulder, 1985, 1992; Richards & Casey, 1991; Weber, van der Molen, & Molenaar, 1994). In anesthesiology, attempts have been made to use heart rate variability as an index of depth of anesthesia (Baumert, Frey, & Adt, 1995). Whatever the focus of the study, however, putative autonomic mechanisms are generally invoked as mediators of these relationships (Binkley et al., 1995; Deutschman, Harris, & Fleisher, 1994; Mulder & Mulder, 1981). Consequently, false inferences about autonomic mediation, based on inadequate evaluation of validity, can hamper a valuable line of research. In fact, the pattern of autonomic control is often the primary interest in many psychophysiological studies of heart rate variability. It is at this most fundamental level that heart rate variability measures must be validated.

Unfortunately, the most direct measures of activity in cardiac autonomic nerves have limited applicability and are associated with methodological and interpretive problems of their own. The effects of anesthesia, invasiveness of the procedures, and limited applicability to broader functional and behavioral contexts severely restrict the utility of this direct approach. Although technically difficult, recording of cardiac autonomic nerve activity may be possible in unanesthetized animals but is not feasible currently in humans.

Despite the difficulty of obtaining direct measures of cardiac nerve traffic, some confirmatory approaches are available and are applicable to humans. Perhaps the most widely applied method is the use of selective pharmacological blockade of the vagal and sympathetic innervations of the heart. The change in the functional state or response of an organ after selective blockade of an autonomic branch, for example, provides an index of the contribution of that branch to the autonomic control of the organ. The change in mean heart period after vagal blockade with atropine has been used often as a criterion index of basal vagal control of the heart. Moreover, the remaining cardiac control after vagal blockade as opposed to combined sympathetic and vagal blockade can serve as an index of residual sympathetic control. The blockade approach has been most useful in elucidating the autonomic origins of various frequency components of heart rate variability (Akselrod

et al., 1985; Cacioppo et al., 1994; Grossman & Kollai, 1993; Katona & Jih, 1975; Koh et al., 1994; Pagani et al., 1986; Pomeranz et al., 1985; Saul et al., 1991) and produces results that are in accord with other measures of sympathetic and parasympathetic control. Pharmacological studies are subject to a wide range of potential biases associated with incomplete blockades, nonspecific or remote receptor actions of the pharmacological agents, and reflexive or other indirect changes in the response system being measured. These complications can be minimized by the judicious selection of drugs and doses and by the use of quantitative methods that permit the assessment of the validity of blockade analyses (Berntson, Cacioppo, & Quigley, 1994).

Another approach that may be useful is the direct microneurographic measurement of activity in sympathetic nerves of the skin and muscle in human participants (e.g., see Eckberg et al., 1985, 1988; Eckberg & Sleight, 1992). The ultimate utility of this method for heart rate variability analyses will depend on the extent to which a close relationship can be demonstrated between cardiac and muscle sympathetic activity among individuals and contexts. Under controlled conditions, sympathetic nerve activities of different organ systems may covary in response to baroreceptor manipulations (Ninomiya, Nisimaru, & Irisawa, 1971). In addition, Wallin et al. (1992) reported significant correlations between muscle sympathetic nerve activity and cardiac norepinephrine spillover at rest, during mental arithmetic, and with isometric handgrip. However, such concordance is not universal (Kingwell et al., 1994), and it will be important to identify the broader range of conditions under which a predictive relationship obtains.

Additional noninvasive indices, although less direct, also may offer independent confirmatory measures of autonomic cardiac control. For example, the duration of the preejection period derived from systolic time intervals has long been considered as an index of sympathetic control of the heart. Because the preejection period is also influenced by ventricular preload and afterload, however, these factors must be controlled or accounted for (e.g., see Cacioppo et al., 1994). An additional consideration is that the preejection period reflects the inotropic state of the heart, whereas sympathetically mediated fluctuations in heart period reflect chronotropic influences. It is uncertain whether and under what conditions inotropic effects predict sympathetic chronotropic actions. Sympathetic inotropic and chronotropic influences do appear to covary during typical cognitive stressors when preload and afterload are held constant (Berntson, Cacioppo, Binkley, et al., 1994).

HF Heart Rate Variability and RSA

RSA is mediated predominantly by parasympathetic influences on the sinus node, and HF heart rate variability is often employed as an index of vagal control. Several aspects of parasympathetic control are relevant to these relationships: (a) central vagal outflow to the heart, (b) mean level of vagal effect on the heart (often referred to as *cardiac vagal tone*), (c) phasic variation of vagal effects on the heart associated with respiration, and (d) dynamic vagal responses affecting R–R interval, including the parasympathetic baroreflex response. These dimensions of parasympathetic cardiac control are often closely related to one another, but they can be dissociated under certain conditions. Moreover, intraindividual and interindividual validations need to be considered separately because factors producing changes in vagal control and RSA may be different within and between individuals (Grossman & Kollai, 1993). Thus, the most relevant gold standards of vagal activity depend on which aspects of parasympathetic control are of interest.

Central vagal outflow. There is no currently available method to evaluate central vagal outflow in humans directly. In animals, however, it is possible to measure central parasympathetic efferent activity from the vagus nerve. Within-subject variations in mean vagal outflow have been shown to be related closely to basal heart period and to heart period fluctuations associated with RSA and baroreceptor activation (Katona, Poitras, Barnett, & Terry, 1970; Koizumi, Terui, & Kollai, 1985; Lumbers, McCloskey, & Potter, 1979). Vagal outflow can be dissociated from RSA if peripheral transduction of efferent outflow is interrupted, for example, by blockade at the sinus node or conduction disturbances that may occur with drugs or clinical disorders (Katona, Lipson, & Danchot, 1977).

Additional factors that may modulate the effects of central vagal outflow to the heart are potential sympathetic–vagal interactions at the sinus node. In anesthetized animals, SA responses to vagus nerve stimulation are proportional to ongoing sympathetic nerve activity, a relation termed *accentuated antagonism* (Levy, 1971). This activity may result from interactions of sympathetic and parasympathetic innervations of the heart (Levy & Warner, 1994), and these interactions may modulate HF heart rate variability in animals (Hedman, Tahvanainen, Hartikainen, & Hakumäki, 1995). With moderate levels of sympathetic activation, autonomic interactions in chronotropic control appear to be minimal when indexed by heart period (Quigley & Berntson, 1996). At extremes of sympathetic activation, sizeable and prolonged attenuation of vagal control of the heart may be mediated by neuropeptides (e.g., neuropeptide Y and galanin) that are colocalized with norepinephrine in sympathetic nerve terminals (Potter et al., 1989; Yang, Senturia, & Levy, 1994). There appear to be considerable species differences in these neuropeptide effects, however, and data are not yet available on their relevance to humans (Potter et al., 1989; Ulman, Moriarity, Potter, & McCloskey, 1993).

Cardiac vagal tone and RSA. Cardiac vagal tone is typically defined as the difference in mean R–R interval between a resting intact baseline and complete vagal blockade. In animals, mean level of vagal effects on R–R interval (cardiac vagal tone) has been assessed by employing a number of techniques, including dissection of the vagus nerve and reversible cooling of the vagus or pharmacological blockade (Katona & Jih, 1975; Rigel, Lipson, & Katona, 1984). In humans, the gold standard for estimating cardiac vagal tone is derived from pharmacological blockade. Vagal tone has been defined as the change in mean R–R interval after atropine (e.g., Jose & Taylor, 1969) or has been derived from the effects of blockade of both autonomic branches (Berntson, Cacioppo, Binkley et al., 1994; Berntson, Cacioppo, & Quigley; 1994; Cacioppo et al., 1994; Grossman & Kollai, 1993).

An advantage of the pharmacological approach is that graduated administration of atropine can reveal a dose–response relationship, which can be used to evaluate the relationship between RSA magnitude and changes in cardiac vagal tone. Studies in humans have indicated that within-subject variations in RSA amplitude mirror changes in cardiac vagal tone across the dose–response function of parasympathetic blockade (Katona & Jih, 1975; Katona et al., 1977; Raczkowska et al., 1983). Conversely, the correspondence between mean R–R intervals and RSA can be evaluated after the contribution of sympathetic influences have been eliminated by cardiac beta-adrenergic blockade. Results reveal that behavioral tasks known to influence cardiac vagal tone produce closely corresponding within-subject changes in mean R–R intervals and RSA, when respiratory parameters are controlled

experimentally or statistically (Grossman et al., 1991; Grossman & Kollai, 1993). This relationship appears to hold even when alterations of cardiac vagal tone are modest (Grossman et al., 1990).

Use of RSA to assess individual differences in cardiac vagal tone is more controversial. A few reports have described very close associations between RSA and atropine-derived measures of cardiac vagal tone (Fouad, Tarazi, Ferrario, Fighaly, & Alicandro, 1984; Hayano et al., 1991). Other investigations, however, have reported lower between-subject correlations among these measures (Grossman & Kollai, 1993; Kollai & Mizsei, 1990; Maciel et al., 1985). The lower correspondence between RSA amplitude and pharmacologically defined vagal tone between participants may be attributable to individual differences in respiratory parameters, respiratory–vagal coupling, or other factors. In view of these findings, caution should be exercised in interpretation of individual differences in vagal tone based on RSA amplitudes. Prediction of individual differences in cardiac vagal tone may be improved by including both RSA and mean R–R interval in the prediction model (Grossman & Kollai, 1993), although results using this approach need to be replicated.

Dynamic parasympathetic baroreflex control. Baroreflex control of efferent vagal effects on R–R interval are mediated by afferent carotid, aortic, and cardiopulmonary baroreceptors that are responsive to short-term systemic blood pressure variations. The baroreflex serves to buffer abrupt blood pressure fluctuations by making vagal outflow to the heart directly proportional to baroreceptor stretch associated with blood pressure. The baroreceptor–cardiac reflex is measured as the R–R response (in milliseconds) per mmHg change in blood pressure. Interindividual correlations between RSA and different measures of baroreflex control are on the order of 0.6 (Bigger & Schwartz, 1994; Grossman, Watkins, Wilhelm, Manolakis, & Lown, 1996). In addition, a linear within-subject relationship has been reported between RSA magnitude and vagal baroreflex response during graded doses of phenylephrine (Zweibel, Bloomfield, & Bigger, 1995). RSA is nearly abolished, however, at very high levels of vagal activity (Anrep et al., 1936a; Eckberg & Orshan, 1977; Goldberger, Ahmed, Parker, & Kadish, 1994). This finding suggests a ceiling effect on respiratory modulation of vagal control of the heart and indicates that RSA and cardiac vagal tone may be dissociated under some conditions. Consequently, caution should be exercised in interpreting RSA at extreme levels of vagal or sympathetic activation (Malik & Camm, 1993).

In summary, RSA appears to be associated with a number of different parasympathetic parameters, including central vagal outflow to the heart, cardiac vagal tone, baroreflex activity, and the phasic respiratory modulation of vagal activity. Consequently, caution needs to be exercised in interpreting RSA, especially for between-subjects comparisons.

LF Heart Rate Variability

The LF R–R and blood pressure rhythms, with a center frequency of about 0.1 Hz, appear to reflect a baroreflex resonance frequency (de Boer et al., 1987; Sleight et al., 1995). The conventional LF bandwidth, however, is considerably broader (0.04 or 0.05–0.15 Hz). This broader bandwidth allows the 0.1-Hz rhythm to be contaminated by RSA, when respiration rate is lower than about 10 breaths/min, and by partial overlap from adjacent slower rhythms that sometimes are observable at a (center) frequency of about 0.03 Hz. These factors present problems for the internal validity of the LF component of heart rate variability and can complicate interpretation.

Scores of published reports have appeared on this LF band of R–R interval variability, but its significance remains controversial. Many authors have assumed that this component of variability provides an index of cardiac sympathetic activation when expressed in normalized units (see Footnote 3) and that the LF/HF ratio offers a measure of sympathovagal balance (Malliani et al., 1994; Pagani et al., 1986). Studies of graded orthostatic challenge, known to increase sympathetic efferent traffic (Burke, Sundlöf, & Wallin, 1977; Iwase, Mano, & Saito, 1987) and decrease vagal outflow, have provided the most consistent evidence of an association between normalized LF power and grade of head-up tilt, although the correlation coefficients are rarely above 0.7 (Bootsma et al., 1994; Montano et al., 1994). Cardiac sympathetic activation induced by exercise, however, has evoked a decrease rather than the expected increase in LF variability, whether calculated in absolute or normalized units (Ahmed, Kadish, Parker, & Goldberger, 1994; Arai et al., 1989; Perini, Orizio, Baselli, Cerutti, & Veicsteinas, 1990).

Other investigations also have failed to find relations between LF power and direct measures of cardiac sympathetic activity in humans. The LF R–R variability, whether expressed in absolute or normalized units, does not change consistently with pharmacological manipulations that enhance or reduce sympathetic adrenergic influences on the heart (Ahmed et al., 1994; Jokkel, Bonyhay, & Kollai, 1995; Kingwell et al., 1994; Saul et al., 1990). In addition, changes in LF variability do not correspond to variations in direct measurements of sympathetic outflow to the heart and periphery (Kingwell et al., 1994; Saul et al., 1990), nor do they significantly correlate with circulating catecholamines (Sloan et al., 1996). Additional studies have clearly indicated that LF rhythms are influenced by both sympathetic and parasympathetic mechanisms (Pomeranz et al., 1985; Saul et al., 1991). Atropine, a selective parasympathetic antagonist, produces a dose–response reduction of LF R–R oscillations, with an eventual elimination of this cardiac rhythm at doses corresponding to complete vagal blockade (Koh et al., 1994). Clearly, the available evidence does not support the use of LF heart rate variability as an index of cardiac sympathetic control or sympathovagal balance, at least not across a range of conditions and groups.

There is considerable evidence for a causal relationship between LF R–R interval rhythms and baroreflex-mediated cardiac vagal responses to arterial blood pressure fluctuations of sympathetic vasomotor origin. Arterial pressure and R–R interval oscillations of about 0.10 Hz (10-s rhythm) are very tightly linked (Cevese, Grasso, Poltronieri, & Schena, 1995). Selective pharmacological blockade of sympathetic efferent traffic to the vasculature reduces the magnitude of 10-s blood pressure and R–R interval oscillations (Scheffer, TenVoorde, Karemaker, & Ros, 1994), indicating that R–R rhythms at this frequency are mediated by vagal baroreflex responses to 0.10-Hz sympathetic vasomotor fluctuations. Similarly, experimentally induced changes in arterial baroreceptor stimulation produce corresponding alterations in LF R–R variability (Bernardi et al., 1994; Koh et al., 1994; Sleight et al., 1995), and exercise-induced changes in LF R–R variability appear to be mediated by vagal baroreflex responses to blood pressure rhythms (Mukai & Hayano, 1995). Baroreflex slopes obtained from cross-spectral analysis of 0.1-Hz fluctuations of systolic pressure and R–R intervals are comparable to slopes obtained after bolus phenylephrine injection (Airaksinen et al., 1997; Watkins, Grossman, & Sherwood, 1996).

Tetraplegic patients, with intact central vagal control of the heart but severed brainstem–spinal sympathetic pathways, still manifest LF R–R rhythms (Koh et al., 1994). Moreover, the response

of LF R–R variability to baroreceptor stimulation is similar to that of normal subjects (Koh et al., 1994). Because descending baroreflex control of sympathetic outflow is abolished in tetraplegics, baroreflex-induced changes in vagal control must be responsible for LF heart rate oscillations. A vagal contribution to LF R–R interval fluctuations is also suggested by their reduction following atropine. Similarly, studies of high spinally transected animals show slow arterial pressure rhythms mediated by spinal sympathetic reflexes, and these pressure oscillations in turn evoke baroreflex-mediated rhythms of cardiac vagal response (Polosa, 1984). This result is in accord with several validated models of human baroreflex mechanisms that account for LF R–R interval oscillations in terms of simple cardiac vagal responses to periodic baroreceptor stimulation (de Boer et al., 1987; Madwed et al., 1989). These models are based on known characteristics of each of the components of the baroreflex (e.g., delays and time constants of vagal and sympathetic responses) and correspond closely to observed behavior of the cardiovascular system.

To summarize, the LF heart rate variability band encompasses a wide range of frequencies that may confound three distinct cardiac rhythms: RSA, 10-s (0.1-Hz) oscillations associated with the baroreflex, and 30-s (0.03-Hz) oscillations. This range complicates interpretation of underlying autonomic indices related to the central frequency (i.e., the 10-s rhythm). The LF heart rate variability has been related consistently to cardiac sympathetic activity or sympathovagal balance primarily with graded orthostatic stimuli. Exercise and adrenergic manipulations fail to reveal clear and reproducible associations with the magnitude of LF oscillations. Rather, LF variability appears to reflect both sympathetic and vagal influences related to baroreflex mechanisms. Changes in the magnitude of LF R–R variability may be due to variations in vagally mediated baroreflex responses brought about by alterations in amplitude of sympathetic blood pressure rhythms or by changes in sensitivity of baroreceptors. To characterize LF R–R interval rhythms more fully, it is necessary to analyze concurrent beat-to-beat arterial pressure.

In conclusion, many validation studies are available to evaluate periodic components of R–R variability as distinct attributes of autonomic control of the heart. They provide a substantive knowledge base that needs to be considered in the interpretation of heart rate variability.

Considerations in the Interpretation of HF Variability

Respiratory parameters. RSA is a product of both peripheral afferents and central respiratory mechanisms (Anrep et al., 1936a, 1936b; see also Berntson, Cacioppo, & Quigley, 1993a). During inspiration, thoracic stretch receptor afferents produce a reflex inhibition of vagal motor outflow, resulting in a phasic increase in heart rate. Although peripheral afferent activity contributes substantially to HF variability, RSA may be apparent even during sustained breath-hold in humans (Hirsch & Bishop, 1981), during apnea in animals (Horner, Brooks, Kozar, Gan, & Philipson, 1995), and after paralysis of respiratory muscles or pulmonary denervation in animals (Hamlin, Smith, & Smetzer, 1966; see also Anrep et al., 1936b). These findings implicate a central respiratory rhythm generator in the origin of HF heart rate variability. The interactions and dynamics of the peripheral and central sources of RSA introduce considerable complexity in the interpretation of HF variability. Within limits, increasing the amplitude of inspiration increases the magnitude of the associated RSA. Hirsch and Bishop (1981), for example, reported a twofold difference in peak-to-valley RSA over tidal volumes of 1.0–3.0 L. In addition, the transfer function that relates heart rate variability to respiratory frequency has a negative slope (Berger et al., 1989; Saul et al., 1989), so that increases in respiratory frequency are associated with a progressive decrease in RSA amplitude (Angelone & Coulter, 1964; Grossman & Kollai, 1993; Hirsch & Bishop, 1981; Saul et al., 1989). In general, a two- to three-fold difference in the amplitude of RSA has been reported for variations in respiratory rate within the typical respiratory frequency range of 0.15–0.4 Hz (Brown et al., 1993; Grossman & Kollai, 1993; Hirsch & Bishop, 1981; Saul et al., 1989). Several authors have argued that the changes in R–R interval power with variations in respiratory frequency do not reflect variations in overall vagal-cardiac nerve traffic because average R–R intervals are nearly constant across all breathing frequencies (Brown et al., 1993; Grossman et al., 1991; Grossman & Kollai, 1993). These findings highlight the importance of respiratory parameters in the interpretation of RSA.

This is an important issue because healthy individuals do not breathe uniformly at fixed frequency and depth (Priban, 1963; van den Aardweg & Karemaker, 1991). In fact, Grossman and Wientjes (1986) reported that, for some individuals, a substantial percentage of breaths may occur at frequencies below 0.15 Hz (9 breaths/min) or above 0.33 Hz (20 breaths/min) and can extend beyond the typical frequency window for RSA. Moreover, experimental conditions such as stress or exercise may alter respiratory parameters substantially. In view of these considerations, it has been suggested that the influence of breathing on RSA must be controlled or accounted for (Bianchi et al., 1990; Brown et al., 1993; Grossman et al., 1991; Grossman, Stemmler, & Meinhardt, 1990). A potential problem with experimental control of breathing is that the requisite mental effort itself may reduce heart rate variability (Patwardhan, Vallurupalli, Evans, Bruce, & Knapp, 1995).

Several groups have compared heart rate variability during spontaneous and controlled breathing. Pagani et al. (1986) reported that controlled metronomic breathing increases both heart rate variability and average R–R intervals, whereas tidal volume (which was not controlled) is slightly greater during spontaneous breathing. These results, however, have not been reproduced by others (Brown et al., 1993; Eckberg, 1983; Hirsch & Bishop, 1981) who have generally reported that rapid breathing reduces rather than increases heart rate variability. Hirsch and Bishop (1981) measured heart rate changes during spontaneous breathing and controlled breathing at constant tidal volumes. They found that heart rate fluctuations during spontaneous breathing were within the 95% confidence limits of those measured during controlled breathing and concluded that voluntary control of breathing does not affect heart rate variability (see also Grossman et al., 1991; Hayano et al., 1994; Madden & Savard, 1995). Patwardhan and coworkers published two seemingly contradictory articles on this subject. In an initial study, Patwardhan, Evans, Bruce, Eckberg, and Knapp (1995) found that power spectra were similar during spontaneous and metronomic breathing at a fixed frequency that corresponded to the spontaneous rate (tidal volume was uncontrolled). In a second study, participants voluntarily reproduced breath-by-breath tidal volumes and respiratory intervals that had been recorded during an earlier period of spontaneous breathing (Patwardhan, Vallurupalli, et al., 1995). In this study, breathing control increased mean heart rate and arterial pressure slightly and reduced low, mid, and respiratory frequency R–R interval power moderately. Inconsistencies in the literature may be due to differences in mental effort involved among different studies. When individuals breathe steadily at a constant rate and tidal volume, as in the study of Hirsch and Bishop (1981), the mental effort involved may be minimal and the

influence on heart rate variability negligible. However, when individuals breathe at constantly changing tidal volumes and respiratory intervals, as in the study of Patwardhan, Vallurupalli, et al. (1995), the mental effort involved may be high, and this effort may lead to reduced heart rate variability. This is an issue that should be investigated further.

Recommendations. In interpreting HF heart rate variability, the potential influence of respiration on RSA must be considered. In general, this consideration calls for the concurrent measurement of respiratory parameters, especially rate because it is a more potent determinant of RSA amplitude than depth within typical breathing ranges. The lack of respiratory measures may not preclude some group contrasts in well-defined populations with known respiratory patterns and large amplitude RSA and when experimental conditions do not alter respiratory parameters appreciably. In most cases, however, measurement of respiratory frequency and depth are recommended, although frequency appears to be a more potent determinant than depth. This method permits identification and exclusion of participants with respiratory rates outside the selected HF variability band. It also allows evaluation of potential biases resulting from differences in respiratory parameters between subject groups or across experimental conditions.

If experimental conditions show significant changes in respiratory parameters, interpretation of associated changes in RSA can be problematic. Two general approaches can be used to adjust for these differences. One is to use respiratory frequency and possibly depth as covariates in statistical analysis or to remove possible contributions by regression prior to analysis (Berntson, Cacioppo, Binkley, et al., 1994; Grossman et al., 1991). An additional approach is to model the expected respiratory contributions to heart rate variability based on established relationships or on parametric investigations of the target population (Grossman et al., 1991; Hirsch & Bishop, 1981; Saul et al., 1989).[9] Although relationships between respiratory parameters and RSA have been examined quantitatively, these studies have generally been pursued with experimentally controlled respiration under restricted conditions. Consequently, a question arises as to the applicability of the derived correction model to a broader range of experimental contexts and conditions. The most straightforward interpretations would be possible when a significant experimental effect is observed both with analysis of the raw data and after extraction of possible respiratory contributions. In this case, it would be possible to rule out the necessary contribution of simple linear respiratory relationships to the experimental effects.

These correction approaches are conservative, however, and may remove actual experimental effects that correlate with respiratory changes. Moreover, the correction procedures assume a unidirectional causal model, in which experimental manipulations alter respiration, more or less directly, and these respiratory alterations then produce secondary changes in RSA. However, respiratory–vagal coupling itself may be altered in specific behavioral contexts because descending projections from rostral neurobehavioral substrates modulate brainstem autonomic mechanisms (e.g., Inui, Nomura, Murase, & Nosaka, 1995; Loewy & Spyer, 1990; Neafsey, 1990). Moreover, it is clear that stressors, even as mild as mental arithmetic, can modulate the sensitivity or set point of the baroreceptor–heart rate reflex (Ditto & France, 1990; Lawler, Sanders, Cox, & O'Connor, 1991; Stephensen, Smith, & Scher, 1981; Steptoe & Sawada, 1989). Because central substrates determine respiratory parameters, it may be overly simplistic to consider covariations between RSA and respiration to be merely secondary to respiratory effects under all conditions (e.g., see Porges, 1995). Clearly, this is a complex issue that calls for additional research. Of particular relevance would be a systematic examination of the impact of respiratory parameters on RSA amplitude during typical psychological tasks and laboratory stressors and under different levels of basal vagal control.

Rather than attempting to adjust for respiratory effects, respiration could be experimentally controlled (Brown et al., 1993; Grossman et al., 1991; Grossman, Stemmler, & Meinhardt, 1990). Moderate control of breathing under basal conditions may have minimal effects on relationships between respiration and heart rate variability. RSA may be altered, however, if respiratory control requires appreciable effort. This alteration could be especially problematic for psychophysiological studies in which experimental manipulations often require considerable mental effort. This is an issue that needs to be considered in studies involving controlled breathing.

Additional caveats and considerations. Early studies identified a respiratory rhythm in the heart rate spectrum that composed the frequency domain representing RSA. Because the spectrum also contained other frequency components, they also were categorized into distinct frequency bands. It is clear that the HF band for adults is usually related to RSA, but the functional and mechanistic bases for segregating other frequency bands are less well established. Moreover, even the common ranges employed for the HF band may not always include the respiratory frequencies for the population being studied. Although 0.15 Hz is often used as the lower cutoff for the HF band, a significant number of individuals show peak respiratory frequencies or a considerable proportion of respiratory power at slightly lower frequencies. For these individuals, RSA will contribute to the variance in lower frequency bands, and HF variability will not provide an accurate quantification of RSA. This problem can be avoided or at least identified by evaluating either the peak of the heart rate spectrum in a broader frequency band to confirm that RSA is included in HF or by calculating the spectrum of respiration.

Additional problems can occur when frequency bands generated for adults are applied to populations with different periodic activity in the heart rate spectrum. Human neonates, for example, have much higher respiratory frequencies than adults, and an appropriate respiratory frequency band must be selected. A related problem with "cardiac aliasing" may arise with some infants or with other populations showing high respiratory frequencies and relatively low heart rates. The Nyquist frequency (half the sampling rate) is the highest frequency signal that can be measured for a given sample rate. Because the respiratory rhythm in heart rate is sampled by each R–R interval, heart rate must be at least twice the respiratory rate to produce the minimum of two R–R intervals per respiratory cycle. With a lower sample rate (heart rate), respiratory frequency fluctuations in heart rate will not be captured reliably, and this variance will appear in lower frequencies as aliasing products. Cardiac aliasing is not a significant problem in normal human adults because heart rates are typically well beyond twice the respiratory frequency. Aliasing, however, may present a problem in some animal studies (Witte, Zwiener, Rother, & Glaser, 1988;

[9]Such a correction could be performed by using a predefined corner frequency near 0.1 Hz (e.g., 20.1 bpm/L for Hirsch & Bishop, 1981; see their Table 3) and the change in RSA with frequency (20.7 dB/decade of frequency for Hirsch & Bishop, 1981, Table 3). These values could be used to normalize the data at the observed respiratory frequencies to a value at a single frequency near the average mean for the age group (e.g., 0.25 Hz for adults).

Zwiener et al., 1994). Rother, Witte, Zwiener, Eiselt, and Fischer (1989) reported that about 20% of their sample of healthy full-term newborns had a mean respiratory rate that exceed half the heart rate. Fortunately, the possibility of cardiac aliasing is easy to identify if concurrent measures of respiration are obtained.

With adequate recording and data processing procedures, control or correction for respiratory parameters, and the appropriate selection of frequency band, variations in HF heart rate variability appear to provide a selective index of vagal control of the heart. As with most psychophysiological measures, RSA is a more accurate index of change than of absolute level. Consequently, within-subject differences among experimental conditions are likely to be more accurate than estimates of the mean or absolute level of vagal control. RSA represents the phasic inspiratory inhibition of vagal outflow, and hence its magnitude is correlated with mean vagal control of the heart. Grossman and Kollai (1993), however, reported that inspiratory inhibition may not be complete at normal respiratory volumes, and the extent of this inhibition may differ from individual to individual. These authors reported close within-subject correspondence between the magnitude of RSA and cardiac vagal tone, as indexed by the change in heart period with vagal blockade. However, a much lower correlation was observed for between-subject comparisons. Potential contributions of age, sex, respiratory parameters, and other individual characteristics need to be considered carefully in interpreting between-subject differences in RSA. In some cases, however, individual differences may reflect actual differences in vagal tone, as in age effects, for example (Jose & Taylor, 1969). In the aggregate, however, these findings suggest caution in inferring absolute levels of mean vagal control across individuals or groups. Even for within-subject contrasts, caution should be exercised in interpreting RSA at extreme levels of vagal or sympathetic activation, given the possibility of ceiling effects or autonomic interactions.

Considerations in Interpretation of LF Variability

The LF variability is a product of both sympathetic and parasympathetic influences on the heart. Consequently, a change in LF power cannot be taken as an index of alterations in sympathetic cardiac control. Some researchers have suggested that the LF/HF ratio may afford an index of the sympathovagal balance, reflecting the relative operating point along a continuum from parasympathetic to sympathetic dominance (Malliani et al., 1994; Pagani et al., 1986). The autonomic branches are not always reciprocally controlled, however, and can vary independently or demonstrate coactivation or coinhibition (Berntson, Cacioppo, & Quigley, 1993b; Berntson, Cacioppo, Quigley, & Fabro, 1994; Koizumi & Kollai, 1992), which raises a question as to the formal status of the construct of sympathovagal balance. Another complexity stems from the fact that parasympathetic contributions to HF and LF variability derive from at least partially distinct mechanisms (respiratory vs. blood pressure–baroreflex processes) and may not be highly correlated under all conditions. The LF variability may serve as a useful clinical marker and may provide an important index of mental effort or other cognitive processes in psychophysiological studies. In the absence of explicit validation over a broad range of conditions, however, the LF/HF ratio cannot be considered as a specific index of sympathetic cardiac control or sympathovagal balance.

Summary Guidelines and Recommendations

Signal Acquisition

Meaningful analysis of heart rate variability is dependent on the integrity of the basic cardiac input signal and the accuracy of R-wave timing. The accuracy of R-wave timing will determine the basic resolution of estimates of variability and limit the size of experimental differences that can be detected. For healthy adult individuals with moderate amplitude variability, a basic digitization rate of 250–500 Hz is suitable, although rates of 500–1000 Hz may be necessary for low-amplitude rhythms in some populations. Even with an adequate digitization rate, R-wave timing can be degraded by noise in the input signal. This timing may require signal filtering or the application of a peak-finding algorithm to improve the localization of the fiducial point. An overall resolution of the entire recording/analytical system of 2–4 ms is adequate for most applications, but a resolution of 1–2 ms is preferable for low-amplitude rhythms. The entire recording system should be calibrated at regular intervals.

Artifacts can seriously corrupt estimates of heart rate variability, so the data processing regimen should include suitable methods to identify and resolve potential artifacts. It is equally important to identify and adequately deal with abnormal beats because they can misguide interpretations of heart rate variability. An occasional abnormal beat can be removed by interpolation, or analyses can be limited to data segments that are free of such anomalies. Records with a high rate of ectopic beats, however, may not be suitable for time-series analyses. In any event, the specific approaches and procedures for dealing with abnormal beats need to be clearly specified, and their potential contributions to the results need to be considered.

Heart Period Versus Heart Rate

Estimates of heart rate variability have been derived from either heart rate or heart period data. Heart period data are preferred on biometic grounds, especially when the interest is in indexing parasympathetic control because the relative linearity between vagal frequency and heart period offers considerable advantage to this metric. The designation *heart rate variability* can be used as a general descriptor, whether the analyses are based on rate or period. It is recommended, however, that the phrase *heart period variability* be used only when referring to results based on heart period data.

Derivation of a Data Series

An R–R interval series, or a beat-by-beat heart rate series, consists of a stream of data points that are unevenly spaced in time. The direct submission of these data series to spectral analysis is not optimal because the results are expressed in cycles/beat and are not easily relatable to the time domain. For analysis of heart rate variability by time-series statistics, the preferred approach is to derive an equal interval time series, in which the data points are equally spaced in time. In generating a time series, it is important that the data be neither undersampled nor oversampled. In general, a sample interval equal to one-fourth of the heart period is appropriate.

Stationarity

Time-series analyses assume that the data show at least weak stationarity, having a stable mean and variance over time. Stationarity is a problematic issue because violations in actual heart period data may be quite common. It is important to minimize nonstationarities to the extent possible by maintaining a constant and controlled testing context. One approach to dealing with residual nonstationarities is to select stationary data segments for analysis. A concern over this approach is that the prevalence of nonstationarities may result in samples that are not representative of the data as a whole. An alternative approach is to remove slower nonstationary trends

based on linear or more complex (e.g., polynomial) models. The target cardiac rhythm itself may vary over time, however, and this inherent nonstationarity cannot be removed or extracted. Approaches to this problem include the analysis of multiple short epochs, within which reasonable stationarity obtains, or the use of approaches explicitly designed to characterize nonstationary signals (e.g., modified Wigner distributions, moving periodograms, wavelet transforms, or short-term FFTs). Although moderate violations of stationarity may not seriously affect estimates of heart period variability under some conditions, the issue of stationarity is important and should not be ignored.

Selection of Appropriate Analytical Epochs

To minimize nonstationarities, it is generally desirable to avoid prolonged analytical epochs. Cardiac rhythms may vary from cycle to cycle, however, and recordings should be sufficiently long to sample short-term variations adequately. A recording duration of at least 10 times the wavelength of the lowest frequency of interest has been recommended (see Task Force, 1996). Based on this criterion, 1-min recording epochs are recommended to assess the HF component of heart rate variability (0.15–0.4 Hz), and 2 min are needed for the LF band (0.05–0.15 Hz). When desired, replicate recordings could be obtained over contiguous or temporally discrete epochs (see Footnote 8).

Analytical Methods

A number of approaches are currently available for analyzing periodic components of heart rate variability; the FFT, AR modeling, the moving polynomial method, and the peak-to-valley statistic are among the most common. Each of these methods can provide valid estimates of periodic components of heart rate variability when the target rhythm is sinusoidal and the data are stationary, and direct comparisons have revealed generally comparable results. Each of these approaches has advantages and disadvantages, and no consensus has emerged on a single optimal analytic method.

Caveats in Interpreting Heart Rate Variability

The RSA is mediated predominantly by parasympathetic influences on the sinus node, and HF heart rate variability is often employed as an index of vagal control of the heart. There are many caveats in such interpretations. Ceiling and floor effects, interactions among the autonomic branches, cardiac or neural abnormalities, and variations in respiratory parameters can degrade predictive relationships between RSA and vagal outflow. In particular, respiratory parameters are important determinants of RSA and may have substantial impact on HF variance independent of changes in cardiac vagal tone. Consequently, potential contributions of respiration must be considered in interpretations of RSA. It is also important to ensure that respiratory frequencies fall within the selected HF band and that this band does not include appreciable LF power. In general, within-subject variations in HF variability appear to be more closely related to variations in vagal control than do between-subject differences because age, sex, and other individual characteristics may be important determinants of RSA amplitude. At best, HF variability affords only an indirect and imprecise measure of vagal control, and interpretations should be tempered appropriately.

In contrast to HF variability, both autonomic branches contribute to LF heart rate variability. Consequently, LF variability does not constitute a specific index of either autonomic branch. Although LF power may covary with sympathetic control under limited conditions, the available data do not support the use of either LF variability or the ratio of LF-to-HF variability as a general index of sympathetic cardiac control or sympathovagal balance.

Future Directions

This report recognizes the importance of heart rate variability as a tool for assessing the integrity of the autonomic nervous system, the interaction between psychological states and autonomic control, and the pathophysiology of diseases that involve or are influenced by autonomic function. In recommending that large longitudinal studies include measures of heart rate variability to delineate its clinical significance, the Task Force (1996) also affirmed that this noninvasive measure provides important information about cardiovascular function in health and disease not otherwise available. The present report extends that affirmation to psychophysiological research.

Psychology and physiology are interwoven inextricably. Psychological processes are also physiological processes; they cannot be understood fully without detailed consideration of the structural and functional aspects of the neuroendocrine and nervous systems. Similarly, many physiological systems cannot be understood completely without a consideration of the role of psychological and behavioral processes in the operations of these systems. However, the complexities of these interactions often seem daunting. Because the methods for deriving heart rate variability are noninvasive, they provide a window through which some of these complexities can be studied without perturbing the underlying systems. Measures of heart rate variability possess an additional, highly desirable feature: they are easily obtained with sophisticated, commercially available instruments for clinical applications and research. Thus, it is not surprising that an extensive literature is available on the mechanisms underlying heart rate variability and on relationships between heart rate variability and psychological states and processes. Although the widespread application of these measures serves as an indication of their potential merit, resolution of a number of issues would enhance the value of heart rate variability as a clinical and research tool.

First, it is important to advance the status of heart rate variability measures from psychophysiological *outcomes* of a state or process to *markers* of that state or processes (Cacioppo & Tassinary, 1990). Both outcomes and markers capture the predictive relation from a psychological variable to a physiological response. The state of a psychophysiological marker, however, also permits inferences concerning the psychological variable, whereas outcome measures do not. The mere fact that a psychological event is associated with change in heart rate variability is not sufficient to infer that psychological event from the occurrence of the variability change. Markers permit stronger inferences than do outcome measures. At this point, RSA can be considered as a marker of vagal control of the heart. If variables such as respiratory rate and depth, age, and other known determinants are taken into account, a change is RSA can be used meaningfully to index changes in vagal control. There are two related approaches to the development of psychophysiological markers of *psychological* processes. One is to identify more thoroughly the psychological determinants of heart rate variability, and another is to elucidate the physiological mechanisms that underlie the relations between psychological processes and cardiac rhythms. Both of these approaches would foster the development of more comprehensive theories and models of psychophysiological relationships, identify relevant organizing dimensions, and clarify extraneous influences that need to be controlled or accounted for in psychophysiological studies.

A related area that deserves attention is the further development of criterion measures of psychological processes. A close predictive relation between a psychological variable and a pattern of heart rate variability could not be expected if there is appreciable error variance in the psychological measure. For example, although baseline heart rate variability can be highly reproducible over time, temporal reproducibility of variability indices for stress reactivity may be considerably poorer (Sloan, Shapiro, Bagiella, Gorman, & Bigger, 1995). This difference does not necessarily imply a lack of relationship between stress and heart rate variability, however, because stress reactions to an identical stimulus may change over time and may do so differentially across individuals. In the absence of a criterion measure of stress, these changes would appear as error variance. This problem is exacerbated for comparisons among studies because significant variations are possible in the potency of stressors employed, methods of delivery, and their duration. In view of these considerations, independent, criterion measures of psychological states or processes would be of considerable benefit in identifying and validating psychophysiological relationships. In the absence of stable criterion measures, meaningful analyses may be limited to group effects.

Analytical methods also warrant further development and standardization. Although reproducibility of resting heart rate variability can be very high when a single system is used by trained staff, analysis of identical data by different commercially available systems may lead to substantially different results (Jung et al., 1996). Differences in outcomes and interpretations of data from otherwise similar studies can only lead to confusion and impede progress. Analysis of heart rate variability is methodologically difficult and is fraught with pitfalls. The present recommendations and guidelines should help to standardize methods and improve the accuracy of heart rate variability measures. Continued research and development on analytical methods are important to enhance the accuracy of measures further and more effectively quantify time-varying changes in heart rate variability. Also helpful would be methods for calibrating the analytical processes of different laboratories to a common standard. Such a standard would require a suitable data set, with known characteristics, that could serve as a tool for calibrating performance of an analysis system and its operators.

Ideally, this data set would be simulated by computer, so that the variance components could be specified precisely. The set should be comprised of data that approximate the ranges of heart rate, heart rate variability, artifact levels, nonstationarities, and other dimensions that could be encountered in actual populations. The data set would minimally be comprised of R–R interval series or, better yet, of simulations of digitized ECG records. These records could be processed by an analytical system, and the precise performance of the system could then be specified against an absolute standard. This process would be analogous to the practice of calibrating biochemical assay laboratories to establish internal and external validity. The availability of a standard data set would not preclude development of new or advanced systems because their attributes could be understood in relation to the established standards, thus providing for orderly evolution of improved systems.

In summary, patterns of heart rate variability hold considerable promise as psychophysiological measures and have already proved useful in psychophysiological applications. Further developments in measurement and analysis of cardiac rhythms and advances in concepts and metrics of psychological processes would foster further psychophysiological applications of heart rate variability. A multifactorial, interdisciplinary approach, at both the physiological and psychological levels, would undoubtedly contribute to the development of the field.

REFERENCES

Airaksinen, K. E. J., Tahvanainen, K. U. O., Kussela, T. A., Huikuri, H. V., Niemelä, M. J., Karjalainen, P., & Eckberg, D. L. (1997). Cross spectral analysis in assessment of baroreflex gain in patients with coronary artery disease. *Annals of Noninvasive Electrocardiology* (in press).

Ahmed, M. W., Kadish, A. H., Parker, M. A., & Goldberger, J. J. (1994). Effect of physiologic and pharmacologic adrenergic stimulation on heart rate variability [see comments]. *Journal of the American College of Cardiology, 24*, 1082–1090.

Akselrod, S., Gordon, D., Madwed, J. B., Snidman, N. C., Shannon, D. C., & Cohen, R. J. (1985). Hemodynamic regulation: Investigation by spectral analysis. *American Journal of Physiology, 18*, H867–H875.

Akselrod, S., Gordon, D., Ubel, F. A., Shannon, D. C., Barger, A. C., & Cohen, R. J. (1981). Power spectrum analysis of heart rate fluctuations: A quantitative probe of beat-to-beat cardiovascular control. *Science, 213*, 220–222.

Albrecht, P., Cohen, R. J., & Mark, R. G. (1988). A stochastic characterization of chronic ventricular ectopic activity. *IEEE Transactions on Biomedical Engineering, 35*, 539–550.

Angelone, A., & Coulter, N. A. (1964). Respiratory sinus arrhythmia: A frequency dependent phenomenon. *Journal of Applied Physiology, 19*, 479–482.

Anrep, G. V., Pascual, W., & Rössler, R. (1936a). Respiratory variations of the heart rate. I. The reflex mechanism of the respiratory arrhythmia. *Proceedings of the Royal Society of London B, 119*, 191–217.

Anrep, G. V., Pascual, W., & Rössler, R. (1936b). Respiratory variations in heart rate. II. The central mechanism of the sinus arrhythmia and the inter-relationships between central and reflex mechanisms. *Proceedings of the Royal Society of London B, 119*, 218–230.

Arai, Y., Saul, J. P., Albrecht, P., Hartley, H., Lilly, L. S., Cohen, R. J., & Colucci, W. S. (1989). Modulation of autonomic activity during and immediately after exercise. *American Journal of Physiology, 256*, H132–H141.

Bainbridge, F. A. (1920). The relation between respiration and the pulse-rate. *Journal of Physiology, 54*, 192–202.

Barbieri, R., Waldmann, R. A., DiVirgilio, V., Triedman, J. K., Bianchi, A. M., Cerutti, S., & Saul, J. P. (1996). Continuous quantification of baroreflex and respiratory control of heart rate by use of bivariate autoregressive techniques. *Annals of Noninvasive Electrocardiography, 1*, 264–277.

Bartoli, F., Baselli, G., & Cerutti, S. (1982). Application of identification and linear filtering algorithms to the R–R interval measurements. *Computers in Cardiology, 9*, 485–488.

Baselli, G., Cerutti, S., Civardi, S., Lombardi, F., Malliani, A., Merri, M., Pagani, M., & Rizzo, G. (1987). Heart rate variability signal processing: A quantitative approach as an aid to diagnosis in cardiovascular pathologies. *International Journal of Bio-medical Computing, 20*, 51–70.

Baumert, J. H., Frey, A. W., & Adt, M. (1995). Analysis of heart rate variability. Background, method, and possible use in anesthesia. *Anaesthetist, 44*, 677–686.

Berger, R. D. (1987). *Analysis of the cardiovascular control system using broad-band stimulation*. Unpublished doctoral thesis, Massachusetts Institute of Technology, Cambridge.

Berger, R. D., Akselrod, S., Gordon, D., & Cohen R. J. (1986). An efficient algorithm for spectral analysis of heart rate variability. *IEEE Transactions on Biomedical Engineering, 33*, 900–904.

Berger, R. D., Saul, J. P., & Cohen, R. J. (1989). Transfer function analysis of autonomic regulation: I. The canine atrial rate response. *American Journal of Physiology, 256*, H142–H152.

Bernardi, L., Keller, F., Sanders, M., Reddy, P. S., Meno, F., & Pinsky,

M. R. (1989). Respiratory sinus arrhythmia in the denervated human heart. *Journal of Applied Physiology, 67*, 1447–1455.

Bernardi, L., Leuzzi, S., Radaelli, A., Passino, C., Johnston, J. A., & Sleight, P. (1994). Low-frequency spontaneous fluctuations of R-R interval and blood pressure in conscious humans: A baroreceptor or central phenomenon? *Clinical Science, 87*, 649–654.

Bernardi, L., Rossi, M., & Ricordi, L. (1992). Clinical assessment of respiratory sinus arrhythmia by computerized analysis of RR interval and respiration. *Gionale Italiano di Cardiologia, 22*, 517–529.

Bernardi, L., Salvucci, F., Suardi, R., Solda, P. L., Calciati, A., Perlini, S., Falcone, C., & Ricciardi, L. (1990). Evidence for an intrinsic mechanism regulating heart rate variability in the transplanted and the intact heart during submaximal dynamic exercise? *Cardiovascular Research, 24*, 969–981.

Berntson, G. G., Cacioppo, J. T., Binkley, P. F., Uchino, B. N., Quigley, K. S., & Fieldstone, A. (1994). Autonomic cardiac control: III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockades. *Psychophysiology, 31*, 599–608.

Berntson, G. G., Cacioppo, J. T., & Quigley, K. S. (1993a). Respiratory sinus arrhythmia: Autonomic origins, physiological mechanisms, and psychophysiological implications. *Psychophysiology, 30*, 183–196.

Berntson, G. G., Cacioppo, J. T., & Quigley, K. S. (1993b). Cardiac psychophysiology and autonomic space in humans: Empirical perspectives and conceptual implications. *Psychological Bulletin, 114*, 296–322.

Berntson, G. G., Cacioppo, J. T., & Quigley, K. S. (1994). Autonomic cardiac control. I. Estimation and validation from pharmacological blockades. *Psychophysiology, 31*, 572–585.

Berntson, G. G., Cacioppo, J. T., & Quigley, K. S. (1995). The metrics of cardiac chronotropism: Biometric perspectives. *Psychophysiology, 32*, 162–171.

Berntson, G. G., Cacioppo, J. T., Quigley, K. S., & Fabro, V. J. (1994). Autonomic space and psychophysiological response. *Psychophysiology, 31*, 44–61.

Berntson, G. G., Quigley, K. S., Fabro, V. T., & Cacioppo, J. T. (1992). Vagal stimulation and cardiac chronotropy in rats. *Journal of the Autonomic Nervous System, 41*, 221–226.

Berntson, G. G., Quigley, K. S., Jang, J., & Boysen, S. T. (1990). An approach to artifact identification: Application to heart period data. *Psychophysiology, 27*, 586–598.

Berntson, G. G., & Stowell, J.R. (in press). ECG artifacts and heart period variability: Don't miss a beat! *Psychophysioloy*.

Bianchi, A., Bontempi, B., Cerutti, S., Gianooglio, P., Comi, G., & Natali Sora, M. G. (1990). Spectral analysis of heart rate variability signal and respiration in diabetic subjects. *Medical and Biological Engineering and Computing, 28*, 205–211.

Bigger, J. T., Jr., Fleiss, J. L., Steinman, R. C., Rolnitzky, L. M., Kleiger, R. E., & Rottman, J. N. (1992). Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation, 85*, 164–171.

Bigger, J. T., Jr., Fleiss, J. L., Steinman, R. C., Rolnitzky, L. M., Schneider, W., & Stein, P. K. (1995). RR variability in healthy, middle-aged persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. *Circulation, 91*, 1936–1943.

Bigger, J. T., Jr., Rolnitzky, L. M., Steinman, R. C., & Fleiss, J. L. (1994). Predicting mortality after myocardial infarction from the response of RR variability to antiarrhythmic drug therapy. *Journal of the American College of Cardiology, 23*, 733–740.

Bigger, J. T., Jr., & Schwartz, P. J. (1994). Markers of vagal activity and the prediction of cardiac death after myocardial infarction. In M. N. Levy & P. J. Schwartz (Eds.), *Vagal control of the heart: Experimental basis and clinical implications* (pp. 481–508). Armonk, NY: Futura Publishing.

Bigger, J. T., Jr., Steinman, R. C., Rolnitzky, L. M., Fleiss, J. L., Albrecht, P., & Cohen, R. J. (1996). Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. *Circulation, 93*, 2142–2151.

Binkley, P. F., Orsinelli, D. A., Nunziata, E., Patterson, S. P., Khot, U. N., Puri, R., Latcham, A. P., & Pearson, A. C. (1995). Differing autonomic response to dobutamine in the presence and absence of ischemia: Implications for the autonomic contribution to positive inotropic intervention. *American Heart Journal, 130*, 1054–1061.

Bonaduce, D., Marciano, F., Petretta, M., Migaux, M. L., Morgano, G., Bianchi, V., Salemme, L., Valva, G., & Condorelli, M. (1994). Effects of converting enzyme inhibition on heart period variability in patients with acute myocardial infarction. *Circulation, 90*, 108–113.

Bootsma, M., Swenne, C. A., Van Bolhuis, H. H., Chang, P. C., Cats, V. M., & Bruschke, A. V. (1994). Heart rate and heart rate variability as indexes of sympathovagal balance. *American Journal of Physiology, 266*, H1565–H1571.

Borst, C., & Karemaker, J. M. (1983). Time delays in the human baroreceptor reflex. *Journal of the Autonomic Nervous System, 9*, 399–409.

Brillinger, D. R. (1975). *Time series: Data analysis and theory*. New York: Holt, Reinhart, and Winston.

Brockwell, P. J., & Davis, R. A. (1991). *Time series: Theory and methods*. New York: Springer-Verlag.

Brown, T. E., Beightol, L. A., Koh, J., & Eckberg, D. L. (1993). The important influence of respiration on human R–R interval power spectra is largely ignored. *Journal of Applied Physiology, 75*, 2310–2317.

Burke, D., Sundlöf, G., & Wallin, B. G. (1977). Postural effects on muscle nerve sympathetic activity in man. *Journal of Physiology, 272*, 399–414.

Burkholder, T., Chambers, M., Hotmire, K., Wurster, R. D., Moody, S., & Randall, W. C. (1992). Gross and microscopic anatomy of the vagal innervation of the rat heart. *Anatomical Record, 232*, 444–452.

Byrne, E. A., & Porges, S. W. (1993). Data-dependent filter characteristics of peak-valley respiratory sinus arrhythmia estimation: A cautionary note. *Psychophysiology, 30*, 397–404.

Cacioppo, J. T., Berntson, G. G., Binkley, P. F., Quigley, K. S., Uchino, B. N., & Fieldstone, A. (1994). Autonomic cardiac control. II. Basal response, noninvasive indices, and autonomic space as revealed by autonomic blockades. *Psychophysiology, 31*, 586–598.

Cacioppo, J. T., & Tassinary, L. G. (1990). Inferring psychological significance from physiological signals. *American Psychologist, 45*, 16–28.

Carlson, M. D., Geha, A., Hsu, J., Martin, P. M., Levy, M., Jacobs, G., & Waldo, A. L. (1992). Selective stimulation of parasympathetic nerve fibers to the human sinoatrial node. *Circulation, 85*, 1311–1317.

Carlsten, A., Folkow, B., & Hamberger, C.-A. (1957). Cardiovascular effects of direct vagal stimulation in man. *Acta Physiologica Scandinavica, 41*, 68–76.

Cevese, A., Grasso, R., Poltronieri, R., & Schena, F. (1995). Vascular resistance and arterial pressure low-frequency oscillations in the anesthetized dog. *American Journal of Physiology, 268*, H7–H16.

Chatfield, C. (1989). *The analysis of time series, an introduction* (4th ed.). London: Chipman & Hall.

Cherniack, N. S., & Longobardo, G. S. (1973). Cheyne–Stokes breathing—An instability in physiologic control. *New England Journal of Medicine, 288*, 952–957.

Chess, G. F., Tam, R. M. K., & Calaresu, F. R. (1975). Influence of cardiac neural inputs on rhythmic variations of heart period in the cat. *American Journal of Physiology, 228*, 775–780.

Cheung, M. N. (1981). Detection and recovery from errors in cardiac interbeat intervals. *Psychophysiology, 18*, 341–346.

Coker, R., Koziell, A., Oliver, C., & Smith, S. E. (1984). Does the sympathetic nervous system influence sinus arrhythmia in man? Evidence from combined autonomic blockade. *Journal of Physiology, 356*, 459–464.

Daffonchio, A., Franzelli, C., Radaelli, A., Castiglioni, P., Di Rienzo, M., Mancia, G., & Ferrari, A. U. (1995). Sympathectomy and cardiovascular spectral components in conscious normotensive rats. *Hypertension, 25*, 1287–1293.

de Boer, R. W., Karemaker, J. M., & Strackee, J. (1984). Comparing spectra of a series of point events particularly for heart rate variability data. *IEEE Transactions on Biomedical Engineering, 31*, 384–387.

de Boer, R. W., Karemaker, J. M., & Strackee, J. (1985). Description of heart-rate variability data in accordance with a physiological model for the genesis of heart beats. *Psychophysiology, 22*, 147–155.

de Boer, R. W., Karemaker, J. M., & Strackee, J. (1987). Hemodynamic fluctuations and baroreflex sensitivity in humans: A beat-to-beat model. *American Journal of Physiology, 253*, H680–H689.

Deutschman, C. S., Harris, A. P., & Fleisher, L. A. (1994). Changes in heart rate variability under propofol anesthesia: A possible explanation for propofol-induced bradycardia. *Anesthesia and Analgesia, 79*, 373–777.

Dexter, F., Levy, M. N., & Rudy, Y. (1989). Mathematical model of the changes in heart rate elicited by vagal stimulation. *Circulation Research, 65*, 1330–1339.

Di Rienzo, M., Castiglioni, P., Parati, G., Mancia, G., & Pedotti, A. (1996). Effects of sino-aortic denervation on spectral characteristics of blood pressure and pulse interval variability: A wide-band approach. *Medical and Biological Engineering and Computing, 34*, 133–141.

Ditto, B., & France, C. (1990). Carotid baroreflex sensitivity at rest and

during psychological stress in offspring of hypertensives and non-twin sibling pairs. *Psychosomatic Medicine, 52*, 610–620.

Donders, F. C. (1868). Zur Physiologie des Nervus vagus. *Pflüger Archiv für die gesammte Physiologie, 1*, 331–361.

Dykes, F. D., Ahmann, P. A., Baldzer, K., Carrigan, T. A., Kitney, R., & Giddens, D. P. (1986). Breath amplitude modulation of heart rate variability in normal full-term neonates. *Pediatric Research, 20*, 301–308.

Eckberg, D. L. (1976). Temporal response patterns of the human sinus node to brief carotid baroreceptor stimuli. *Journal of Physiology, 258*, 769–782.

Eckberg, D. L. (1980). Nonlinearities of the human carotid baroreceptor–cardiac reflex. *Circulation Research, 47*, 208–216.

Eckberg, D. L. (1983). Human sinus arrhythmia as an index of vagal cardiac outflow. *Journal of Applied Physiology, 54*, 961–966.

Eckberg, D. L. (1995). Respiratory sinus arrhythmia and other human cardiovascular periodicities. In J. A. Dempsey & A. I. Pack (Eds.), *Regulation of breathing* (pp. 669–740). New York: Marcel Dekker.

Eckberg, D. L. (in press). Sympathovagal balance. A critical appraisal. *Circulation*.

Eckberg, D. L., & Eckberg, M. J. (1982). Human sinus node responses to repetitive, ramped carotid baroreceptor stimuli. *American Journal of Physiology, 242*, H638–H644.

Eckberg, D. L., Kifle, Y. T., & Roberts, V. L. (1980). Phase relationship between normal human respiration and baroreflex responsiveness. *Journal of Physiology, 304*, 489–502.

Eckberg, D. L., Nerhed, C., & Wallin, B. G. (1985). Respiratory modulation of muscle sympathetic and vagal cardiac outflow in man. *Journal of Physiology, 365*, 181–196.

Eckberg, D. L., & Orshan, C. R. (1977). Respiratory and baroreceptor reflex interactions in man. *Journal of Clinical Investigation, 59*, 780–785.

Eckberg, D. L., Rea, R. F., Andersson, O. K., Hedner, T., Pernow, J., Lundberg, J. M., & Wallin, B. G. (1988). Baroreflex modulation of sympathetic activity and sympathetic neurotransmitters in humans. *Acta Physiologica Scandinavica, 133*, 221–231.

Eckberg, D. L., & Sleight, P. (1992). *Human baroreflexes in health and disease*. Oxford: Clarendon.

Eppinger, H., & Hess, L. (1915). *Vagotonia: A clinical study in vegetative neurology* (W. M. Kraus & S. E. Jelliffe, Trans.). New York: The Nervous and Mental Disease Publishing Co.

Erschler, I. (1988). Willem Einthoven—The man. *Archives of Internal Medicine, 148*, 453–455.

Faes, J. C., De Neeling, N. N. D., Kingma, R., TenVoorde, B. J., & Karemaker, J. M. (1995). On the quantification of heart rate change in autonomic function tests: Relations between measures in beats per minute, seconds and dimensionless ratios. *Clinical Science, 89*, 557–564.

Fahrenberg, J., & Foerster, F. (1991). A multiparameter study in non-invasive cardiovascular assessment. *Journal of Psychophysiology, 5*, 145–158.

Felder, R. B., & Mifflin, S. W. (1994). Baroreceptor and chemoreceptor afferent processing in the solitary tract nucleus. In I. R. A. Barraco (Ed.), *Nucleus of the solitary tract* (pp. 169–185). Boca Raton, FL: CRC Press.

Fernandez de Molina, A., & Perl, E. R. (1965). Sympathetic activity and the systemic circulation in the spinal cat. *Journal of Physiology, 181*, 82–102.

Fouad, F. M., Tarazi, R. C., Ferrario, C. M., Fighaly, S., & Alicandro, C. (1984). Assessment of parasympathetic control of heart rate by a non-invasive method. *American Journal of Physiology, 246*, H838–H842.

Friesen, G. M., Jannett, T. C., Jadalloh, M. A., Yates, S. L., Quint, S. R., & Nogle, H. T. (1990). A comparison of the noise sensitivity of nine QRS detection algorithms. *IEEE Transactions on Biomedical Engineering, 37*, 85–98.

Glass, L., & Mackey, M. C. (1988). *From clocks to chaos*. Princeton, NJ: Princeton University Press.

Goldberger, A. (1992). Fractal mechanisms in the electrophysiology of the heart. *IEEE Engineering in Medicine and Biology Magazine, 11*, 47–52.

Goldberger, A. L., Findley, L. J., Blackburn, M. R., & Mandell, J. A. (1984). Nonlinear dynamics in heart failure: Implications of long-wavelength cardiopulmonary oscillations. *American Heart Journal, 107*, 612–615.

Goldberger, J. J., Ahmed, M. W., Parker, M. A., & Kadish, A. H. (1994). Dissociation of heart rate variability from parasympathetic tone. *American Journal of Physiology, 266*, H2152–H2157.

Graham, F. K. (1978). Constraints on measuring heart rate and period sequentially through real and cardiac time. *Psychophysiology, 15*, 492–495.

Grossman, P. (1992a). Breathing rhythms of the heart in a world of no steady state: A comment on Weber, Molenaar, and van der Molen. *Psychophysiology, 29*, 66–72.

Grossman, P. (1992b). Respiratory and cardiac rhythms as windows to central and autonomic biobehavioral regulation: Selection frames, keeping the panes clean and viewing neural topography. *Biological Psychology, 34*, 131–161.

Grossman, P., Karemaker, J., & Wieling, W. (1991). Prediction of tonic parasympathetic cardiac control using respiratory sinus arrhythmia: The need for respiratory control. *Psychophysiology, 28*, 201–216.

Grossman, P., & Kollai, M. (1993). Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: Within- and between-subject relations. *Psychophysiology, 30*, 486–495.

Grossman, P., Stemmler, G., & Meinhardt, E. (1990). Paced respiratory sinus arrhythmia as an index of cardiac parasympathetic tone during varying behavioral tasks. *Psychophysiology, 27*, 404–416.

Grossman, P., & Svebak, S. (1987). Respiratory sinus arrhythmia as an index of parasympathetic cardiac control. *Psychophysiology, 24*, 228–235.

Grossman, P., van Beek, J., & Wientjes, C. (1990). A comparison of three quantification methods for estimation of respiratory sinus arrhythmia. *Psychophysiology, 27*, 702–714.

Grossman, P., Watkins, L. L., Wilhelm, F. H., Manolakis, D., & Lown, B. (1996). Cardiac vagal control and dynamic responses to psychological stressors among coronary artery disease patients. *American Journal of Cardiology, 78*, 1424–1427.

Grossman, P., & Wientjes, K. (1986). Respiratory sinus arrhythmia and parasympathetic cardiac control: Some basic issues concerning quantification, applications and implications. In P. Grossman, K. H. L. Janssen, & D. Vaitl (Eds.), *Cardiorespiratory and cardiosomatic psychophysiology* (pp. 117–138). New York: Plenum Press.

Guyton, A. C., & Harris, J. W. (1951). Pressoreceptor—Autonomic oscillation: A probable cause of vasomotor waves. *American Journal of Physiology, 165*, 158–169.

Guzzetti, S., Cogliati, C., Broggi, C., Carozzi, C., Caldiroli, D., Lombardi, F., & Malliani, A. (1994). Influences of neural mechanisms on heart period and arterial pressure variabilities in quadriplegic patients. *American Journal of Physiology, 266*, H1112–H1120.

Hales, S. (1733). *Statical essays: Containing haemastaticks; or, An account of some hydraulick and hydrostatical experiments made on the blood and blood-vessels of animals*. London: W. Innys, R. Manby, and T. Woodward.

Hamlin, R. L., Smith, C. R., & Smetzer, D. L. (1966). Sinus arrhythmia in the dog. *American Journal of Physiology, 210*, 321–328.

Hayano, J., Mukai, S., Sakakibara, M., Okada, A., Takata, K., & Fujinami, T. (1994). Effects of respiratory interval on vagal modulation of heart rate. *American Journal of Physiology, 267*, H33–H40.

Hayano, J., Sakakibara, Y., Yamada, A., Yamada, M., Mukai, S., Fujinami, T., Yokoyama, K., Watanabe, Y., & Takata, K. (1991). Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *American Journal of Cardiology, 67*, 199–204.

Hedman, A. E., Tahvanainen, K. U., Hartikainen, J. E., & Hakumäki, M. O. (1995). Effect of sympathetic modulation and sympatho–vagal interaction on heart rate variability in anaesthetized dogs. *Acta Physiologica Scandinavica, 155*, 205–214.

Hering, H. E. (1910). A functional test of heart vagi in man. *Menschen München Medizinische Wochenschrift, 57*, 1931–1933.

Hill, M. R., Wallick, D. W., Martin, P. J., & Levy, M. N. (1995). Effects of repetitive stimulation on heart rate and on cardiac vasoactive intestinal polypeptide efflux. *American Journal of Physiology, 268*, H1939–H1946.

Hill-Smith, I., & Purves, R. D. (1978). Synaptic delay in the heart: An iontophoretic study. *Journal of Physiology, 279*, 31–54.

Hille, B. (1992). *Ionic channels of excitable membranes*. Sunderland, MA: Sinauer Associates.

Hirsch, J. A., & Bishop, B. (1981). Respiratory sinus arrhythmia in humans: How breathing pattern modulates heart rate. *American Journal of Physiology, 241*, H620–H629.

Hnatiow, M., & Lang, P. J. (1965). Learned stabilization of cardiac rate. *Psychophysiology, 1*, 330–336.

Hnatkova, K., Copie, X., Staunton, A., & Malik, M. (1995). Numeric processing of Lorenz plots of R–R intervals from long-term ECGs. *Journal of Electrocardiology, 28*(Suppl.), 74–80.

Horner, R. L., Brooks, D., Kozar, L. F., Gan, K., & Philipson, E. A. (1995). Respiratory-related heart rate variability persists during central apnea in dogs: Mechanisms and implications. *Journal of Applied Physiology, 78*, 2003–2013.

Hopf, H.-B., Skyschally, A., Heusch, G., & Peters, J. (1995). Low-frequency spectral power of heart rate variability is not a specific marker of cardiac sympathetic modulation. *Anesthesiology, 82*, 609–619.

Hon, E. H. (1958). The electronic evaluation of the fetal heart rate. *American Journal of Obstetrics and Gynecology, 75*, 1215–1230.

Hon, E. H., & Lee, S. T. (1963). The electronic evaluation of the fetal heart rate. VIII. Patterns preceding fetal death; further observations. *American Journal of Obstetrics and Gynecology, 87*, 814.

Inui, K., Nomura, J., Murase, S., & Nosaka, S. (1995). Facilitation of the arterial baroreflex by the preoptic area in anaesthetized rats. *Journal of Physiology, 488*, 521–531.

Iwase, S., Mano, T., & Saito, M. (1987). Effects of graded head-up tilting on muscle sympathetic activities in man. *The Physiologist, 30*, S62–S65.

Janssen, M. J. A., Swenne, C. A., de Bie, J., Rompelman, O., & van Bemmel, J. H. (1993). Methods in heart rate variability analysis: Which tachogram should we choose? *Computer Methods and Programs in Biomedicine, 41*, 1–8.

James, T. N. (1973). The sinus node as a servomechanism. *Circulation Research, 32*, 307–313.

Japundzic, N., Grichois, M. L., Zitoun, P., Laude, D., & Elghozi, J. L. (1990). Spectral analysis of blood pressure and heart rate in conscious rats: Effects of autonomic blockers. *Journal of the Autonomic Nervous System, 30*, 91–100.

Jennings, J. R., Berg, W. K., Hutcheson, J. S., Obrist, P., Porges, S., & Turpin, G. (1981). Publication guidelines for heart rate studies in man. *Psychophysiology, 18*, 226–231.

Jokkel, G., Bonyhay, I., & Kollai, M. (1995). Heart rate variability after complete autonomic blockade in man. *Journal of the Autonomic Nervous System, 51*, 85–89.

Jose, A. D., & Taylor, R. R. (1969). Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man. *Journal of Clinical Investigation, 48*, 2019–2031.

Jung, J., Heisel, A., Tscholl, D., Fries, R., Schieffer, H., & Ozbek, C. (1996). Assessment of heart rate variability by using different commercially available systems. *American Journal of Cardiology, 78*, 118–120.

Kahneman, D. (1973). *Attention and effort*. Englewood Cliffs, NJ: Prentice-Hall.

Kalsbeek, J. W. H., & Ettema, J. H. (1963). Scored irregularity of the heart pattern and the measurement of perceptual or mental load. *Ergonomics, 6*, 306–307.

Kanters, J. K., Hojgaard, M. V., Agner, E., & Holstein-Rathlou, N. H. (1996). Short- and long-term variations in non-linear dynamics of heart rate variability. *Cardiovascular Research, 31*, 400–409.

Kanters, J. K., Holstein-Rathlou, N. H., & Agner, E. (1994). Lack of evidence for low-dimensional chaos in heart rate variability. *Journal of Cardiovascular Electrophysiology, 5*, 591–601.

Kashyap, R. L. (1980). Inconsistency of the AIC rule for estimating the order of autoregressive models. *IEEE Transactions on Automatic Control, 25*, 996–997.

Katona, P. G., & Jih, F. (1975). Respiratory sinus arrhythmia: A noninvasive measure of parasympathetic cardiac control. *Journal of Applied Physiology, 39*, 801–805.

Katona, P. G., Lipson, D., & Danchot, P. J. (1977). Opposing central and peripheral effects of atropine on parasympathetic cardiac control. *American Journal of Physiology, 232*, H146–H151.

Katona, P. G., Poitras, J. W., Barnett, G. O., & Terry, B. S. (1970). Cardiac vagal efferent activity and heart period in the carotid sinus reflex. *American Journal of Physiology, 218*, 1030–1037.

Kay, S. M., & Marple, S. L. (1981). Spectrum analysis—A modern perspective. *Proceedings of the IEEE, 69*, 1380–1419.

Kezdi, P., & Geller, E. (1968). Baroreceptor control of postganglionic sympathetic nerve discharge. *American Journal of Physiology, 214*, 427–435.

Kingwell, B. A., Thompson, J. M., Kaye, D. M., McPherson, G. A., Jennings, G. L., & Esler, M. D. (1994). Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. *Circulation, 90*, 234–240.

Kitney, R. I. (1975). An analysis of the nonlinear behaviour of the human thermal vasomotor control system. *Journal of Theoretical Biology, 52*, 231–248.

Kitney, R. I. (1980). An analysis of the thermoregulatory influences on heart-rate variability. In R. I. Kitney & O. Rompelman (Eds.), *The study of heart-rate variability* (pp. 81–106). Oxford: Clarendon Press.

Kitney, R. I., & Darvish, N. (1995). Techniques for studying short-term changes in cardio-respiratory data, II. In M. Di Renzo, G. Mancia, G. Parati, A. Pedoni, & A. Zanchetti (Eds.), *Computer analysis of cardiovascular signals* (pp. 41–52). Amsterdam: IOS Press (Ohmsha).

Kleiger, R. E., Miller, J. P., Bigger, J. T., Moss, A. J., & the Multicenter Post-Infarction Research Group. (1987). Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *American Journal of Cardiology, 59*, 256–262.

Koepchen, H. P. (1984). History of studies and concepts of blood pressure waves. In K. Miyakawa, H. P. Koepchen, & C. Polosa (Eds.), *Mechanisms of blood pressure waves* (pp. 3–23). Tokyo: Science Society Press/Springer-Verlag.

Koh, J., Brown, T. E., Beightol, L. A., Ha, C. Y., & Eckberg, D. L. (1994). Human autonomic rhythms: Vagal cardiac mechanisms in tetraplegic subjects. *Journal of Physiology, 474*, 483–495.

Koizumi, K., Ischikawa, T., Nishono, H., & Brooks, C. M. (1975). Cardiac and autonomic system reactions to stretch of the atria. *Brain Research, 87*, 247–261.

Koizumi, K., & Kollai, M. (1992). Multiple modes of operation of cardiac autonomic control: Development of the ideas from Cannon and Brooks to the present. *Journal of the Autonomic Nervous System, 41*, 19–28.

Koizumi, K., Terui, N., & Kollai, M. (1985). Effect of cardiac vagal and sympathetic nerve activity on heart rate in rhythmical fluctuation. *Journal of the Autonomic Nervous System, 12*, 251–259.

Kollai, M., & Mizsei, G. (1990). Respiratory sinus arrhythmia is a limited measure of cardiac parasympathetic control in man. *Journal of Physiology, 424*, 329–342.

Lacey, J. I. (1967). Somatic response patterning and stress: Some revisions of activation theory. In M. H. Appley & R. Trumbull (Eds.), *Psychological stress: Issues in research* (pp. 14–37). New York: Appleton-Century-Crofts.

Lacey, J. I., & Lacey, B. C. (1958). Verification and extension of the principle of autonomic response stereotypy. *American Journal of Psychology, 71*, 50–73.

Lang, P. J., Sroufe, L. A., & Hastings, J. E. (1967). Effects of feedback and instructional set on the control of cardiac rate variability. *Journal of Experimental Psychology, 75*, 425–431.

Lawler, J. E., Sanders, B. J., Cox, R. H., & O'Connor, E. F. (1991). Baroreflex function in chronically stressed borderline hypertensive rats. *Physiology and Behavior, 49*, 539–542.

Levy, M. N. (1971). Sympathetic–parasympathetic interactions in the heart. *Circulation Research, 29*, 437–445.

Levy, M. N., & Warner, M. R. (1994). Parasympathetic effects on cardiac function. In J. A. Armour & J. L. Ardell (Eds.), *Neurocardiology* (pp. 53–76). New York: Oxford University Press.

Levy, M. N., Yang, T., & Wallick, D. W. (1993). Assessment of beat-by-beat control of heart rate by the autonomic nervous system: Molecular biology techniques are necessary, but not sufficient. *Journal of Cardiovascular Electrophysiology, 4*, 183–193.

Levy, M. N., & Zieske, H. (1969). Autonomic control of cardiac pacemaker activity and atrioventricular transmission. *Journal of Applied Physiology, 27*, 465–470.

Linden, W., & Estrin, R. (1988). Computerized cardiovascular monitoring: Method and data. *Psychophysiology, 25*, 227–234.

Litvack D. A., Oberlander, T. F., Carney, L. H., & Saul, J. P. (1995). Time and frequency domain methods for heart rate variability analysis: A methodological comparison. *Psychophysiology, 32*, 492–504.

Loewy, A. D., & Spyer, K. M. (1990). *Central regulation of autonomic functions*. New York: Oxford University Press.

Lombardi, F., Sandrone, G., Pernpruner, S., Sala, R., Garimoldi, M., Cerutti, S., Baselli, G., Pagani, M., & Malliani, A. (1987). Heart rate variability as an index of sympathetic interaction after acute myocardial infarction. *American Journal of Cardiology, 60*, 1239–1245.

Ludwig, C. (1847). Beiträge zur Kenntniss des Einflusses der Respirationsbewegungen auf den Blutlauf im Aortensysteme. *Muller's Archiv für Anatomie, Physiologie, und Wissenschaftliche Medicin*, 242–302.

Lumbers, E. R., McCloskey, D. I., & Potter, E. K. (1979). Inhibition by angiotensin II of baroreceptor-evoked activity in cardiac vagal efferent nerves in the dog. *Journal of Physiology, 294*, 69–80.

Maciel, B. C., Gallo Junior, L., Marin Neto, J. A., Lima Filho, E. C., Terra Filho, J., & Manco, J. C. (1985). Parasympathetic contribution to bradycardia induced by endurance training in man. *Cardiovascular Research, 19*, 642–648.

MacKenzie, J. (1910). *Diseases of the heart* (2nd ed.). London: Oxford Medical Publications.

Madden, K., & Savard, G. K. (1995). Effects of mental state on heart rate and blood pressure variability in men and women. *Clinical Physiology, 15*, 557–569.

Madwed, J. B. (1986). *Dynamic analysis of arterial blood pressure and heart rate during baseline conditions and hemorrhage in the conscious dog*. Unpublished doctoral thesis, Harvard University, Cambridge.

Madwed, J. B., Albrecht, P., Mark, R. G., & Cohen, R. J. (1989). Low-frequency oscillations in arterial pressure and heart rate: A simple computer model. *American Journal of Physiology, 256*, H1573–H1579.

Madwed, J. B., & Cohen, R. J. (1991). Heart rate response to hemorrhage-induced 0.05-Hz oscillations in arterial pressure in conscious dogs. *American Journal of Physiology, 260*, H1248–H1253.

Malik, M. (1995). Geometrical methods for heart rate variability assessment. In M. Malik & A. J. Camm (Eds.), *Heart rate variability* (pp. 47–61). Armonk: Futura Press.

Malik, M., & Camm, A. J. (1990). Significance of long-term components of heart rate variability for the further prognosis after acute myocardiac infarction. *Cardiovascular Research, 24*, 793–803.

Malik, M., & Camm, A. J. (1993). Components of heart rate variability—What they really mean and what we really measure. *American Journal of Cardiology, 72*, 821–822.

Malik, M., Farrell, T., & Camm, A. J. (1990). Circadium rhythm of heart rate variability after acute myocardial infarction and its influence on the prognostic value of heart rate variability. *American Journal of Cardiology, 66*, 1049–1054.

Malik, M., Xia, R., Odemuyiwa, O., Staunton, A., Poloniecki, J., & Camm, A. J. (1993). Influence of the recognition artefact in automatic analysis of long-term electrocardiograms on time-domain measurement of heart rate variability. *Medical and Biological Engineering and Computing, 31*, 539–544.

Malliani, A., Pagani, M., & Lombardi, F. (1994). Physiology and clinical implications of variability of cardiovascular parameters with focus on heart rate and blood pressure. *American Journal of Cardiology, 73*, 3C–9C.

Malliani, A., Pagani, M., Lombardi, F., & Cerutti, S. (1991). Cardiovascular neural regulation explored in the frequency domain. *Circulation, 84*, 482–492.

Mayer, S. (1877). Studien zur Physiologie des Herzens und der Blutgefässe: 5. Abhandlung: Über spontane Blutdruckschwankungen. *Sitzungsberichte der Kaiserlichen Akademie der Wisenschaft Mathemat-Naturwissenschaft Classe, 74*, 281–307.

McCabe, P. M., Yongue, B. G., Ackles, P. K., & Porges, S. W. (1985). Changes in heart period, heart-period variability, and a spectral analysis estimate of respiratory sinus arrhythmia in response to pharmacological manipulations of the baroreceptor reflex in cats. *Psychophysiology, 22*, 195–203.

Merri, M., Arden, D. C., Motley, J. G., & Titlebaum, E. L. (1990). Sampling frequency of the electrocardiogram for spectral analysis of the heart rate variability. *IEEE Transactions on Biomedical Engineering, 37*, 99–106.

Montano, N., Ruscone, T. G., Porta, A., Lombardi, F., Pagani, M., & Malliani, A. (1994). Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. *Circulation, 90*, 1826–1831.

Mukai, S., & Hayano, J. (1995). Heart rate and blood pressure variabilities during graded head-up tilt. *Journal of Applied Physiology, 78*, 212–216.

Mulder, G. (1985). Attention, effort and sinus arrhythmia: How far are we? In J. F. Orlebeke, G. Mulder, & L. J. P. van Dornan (Eds.), *Psychophysiology of cardiovascular control* (pp. 407–424). New York: Plenum Press.

Mulder, G., & Mulder, L. (1981). Information processing and cardiovascular control. *Psychophysiology, 18*, 392–402.

Mulder, L. J. M. (1992). Measurement and analysis methods of heart rate and respiration for use in applied environments. *Biological Psychology, 34*, 205–236.

Murphy, C. A., Sloan, R. P., & Myers, M. M. (1991). Pharmacologic responses and spectral analyses of spontaneous fluctuations in heart rate and blood pressure in SHR rats. *Journal of the Autonomic Nervous System, 36*, 237–250.

Neafsey, E. J. (1990). Prefrontal cortical control of the autonomic nervous system: Anatomical and physiological observations. *Progress in Brain Research, 85*, 147–166.

Ninomiya, I., Nisimaru, N., & Irisawa, H. (1971). Sympathetic nerve activity to the spleen, kidney, and heart in response to baroceptor input. *American Journal of Physiology, 221*, 1346–1351.

Novak, V., Novak, P., Kus, T., & Nadeau, R. (1995). Slow cardiovascular rhythms in tilt and syncope. *Journal of Clinical Neurophysiology, 12*, 64–71.

Obrist, P. A. (1981). *Cardiovascular psychophysiology*. New York: Plenum Press.

Odemuyiwa, O., Malik, M., Farrell, T., Bashir, Y, Poloniecki, J., & Camm, A. J. (1991). A comparison of the predictive characteristic of heart rate variability index and left ventricular ejections fraction for all-cause mortality, arrhythmic events and sudden death after acute myocardial infarction. *American Journal of Cardiology, 68*, 434–439.

Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'Orto, S., Piccaluga, E., Turiel, M., Baselli, G., Cerutti, S., & Maliani, A. (1986). Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho–vagal interaction in man and conscious dog. *Circulation Research, 59*, 178–193.

Parati, G., Castiglioni, P., Di Rienzo, M., Omboni, S., Pedotti, A., & Mancia, G. (1990). Sequential spectral analysis of 24-hour blood pressure and pulse interval in humans. *Hypertension, 16*, 414–421.

Parati, G., Saul, J. P., Di Rienzo, M., & Mancia, G. (1995). Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation: A critical appraisal. *Hypertension, 25*, 1276–1286.

Parer, W. J., & Parer, J. T. (1985). Validity of mathematical methods of quantitating fetal heart rate variability. *American Journal of Obstetrics and Gynecology, 153*, 402–409.

Parker, P., Celler, B. G., Potter, E. K., & McCloskey, D. I. (1984). Vagal stimulation and cardiac slowing. *Journal of the Autonomic Nervous System, 11*, 226–231.

Patwardhan, A. R., Evans, J. M., Bruce, E. N., Eckberg, D. L., & Knapp, C. F. (1995). Voluntary control of breathing does not alter vagal modulation of heart rate. *Journal of Applied Physiology, 78*, 2087–2094.

Patwardhan, A. R., Vallurupalli, S., Evans, J. M., Bruce, E. N., & Knapp, C. F. (1995). Override of spontaneous respiratory pattern generator reduces cardiovascular parasympathetic influence. *Journal of Applied Physiology, 79*, 1048–1054.

Penáz, J. (1962). Frequency response of the cardiac chronotropic action of the vagus in the rabbit. *Archives Internationales de Physiologie, de Biochimie et de Biophysique, 70*, 636–650.

Penáz, J. (1978). Mayer waves: History and methodology. *Automedica*, 2, 135–141.

Peng, C. K., Havlin, S., Hausdorff, J. M., Mietus, J. E., Stanley, H. E., & Goldberger, A. L. (1995). Fractal mechanisms and heart rate dynamics. Long-range correlations and their breakdown with disease. *Journal of Electrocardiology, 28*(Suppl.), 59–65.

Perini, R., Orizio, C., Baselli, G., Cerutti, S., & Veicsteinas, A. (1990). The influence of exercise intensity on the power spectrum of heart rate variability. *European Journal of Applied Physiology, 61*, 143–148.

Pipberger, H. V., Arzbaecher, R. C., Berson, A. S., Briller, S. A., Brody, D. A., Flowers, N. C., Geselowitz, D. B., Lepeschkin, E., Oliver, G. C., Schmitt, O. H., & Spach, M. (1975). Recommendations for standardization of leads and specifications for instruments in electrocardiography and vectorcardiography: Report of the Committee of Electrocardiography, American Heart Association. *Circulation, 52*, 11–31.

Polosa, C. (1984). Central nervous system origin of some types of Mayer waves. In K. Miyakawa, H. P. Koepchen, & C. Polosa (Eds.), *Mechanisms of blood pressure waves* (pp. 277–292). Berlin: Springer.

Pomeranz, B., MaCaulay, R. J. B., Caudill, M. A., Kutz, I., Adam, D., Gordon, D., Kilborn, K. M., Barger, A. C., Shannon, D. C., Cohen, R. J., & Benson, H. (1985). Assessment of autonomic function in humans by heart rate spectral analysis. *American Journal of Physiology, 248*, H151–H153.

Porges, S. W. (1972). Heart rate variability and deceleration as indices of reaction time. *Journal of Experimental Psychology, 92*, 103–110.

Porges, S. W. (1986). Respiratory sinus arrhythmia: Physiological basis, quantitative methods, and clinical implications. In P. Grossman, K. Janssen, & D. Vaitl (Eds.), *Cardiorespiratory and cardiosomatic psychophysiology* (pp. 101–115). New York: Plenum Press.

Porges, S. W. (1995). Orienting in a defensive world: Mammalian modifications of our evolutionary heritage: A polyvagal theory. *Psychophysiology, 32*, 301–318.

Porges, S. W., & Bohrer, R. E. (1990). Analyses of periodic processes in psychophysiological research. In J. T. Cacioppo & L. G. Tassinary (Eds.), *Principles of psychophysiology: Physical, social, and inferential elements* (pp. 708–753). New York: Cambridge University Press.

Porges, S. W., Bohrer, R. E., Cheung, M. N., Drasgow, F., McCabe, P. M., & Keren, G. (1980). New time-series statistic for detecting rhythmic co-occurrence in the frequency domain: The weighted coherence and its application to psychophysiological research. *Psychological Bulletin, 88*, 580–587.

Porges, S. W., & Byrne, E. A. (1992). Research methods for measurement of heart rate and respiration. *Biological Psychology, 34*, 93–130.

Porges, S. W., & Raskin, D. C. (1969). Respiratory and heart rate components of attention. *Journal of Experimental Psychology, 81*, 497–503.

Potter, E. K., Mitchell, L., McCloskey, M. J., Tseng, A., Goodman, A. E., Shine, J., & McCloskey, D. I. (1989). Pre- and postjunctional actions of neuropeptide Y and related peptides. *Regulatory Peptides, 25*, 167–177.

Preiss, G., Iscoe, S., & Polosa, C. (1975). Analysis of a periodic breathing pattern associated with Mayer waves. *American Journal of Physiology, 228*, 768–774.

Preiss, G., & Polosa, C. (1974). Patterns of sympathetic neuron activity associated with Mayer waves. *American Journal of Physiology, 226*, 724–730.

Priban, I. P. (1963). An analysis of some short-term patterns of breathing in man at rest. *Journal of Physiology, 166*, 425–434.

Price, A. D. (1975). Heart rate variability and respiratory concomitants of visual and nonvisual imagery and cognitive style. *Journal of Research in Personality, 9*, 341–355.

Quigley, K. S., & Berntson, G. G. (1996). Autonomic interactions and chronotropic control of the heart: Heart period versus heart rate. *Psychophysiology, 33*, 605–611.

Raczkowska, M., Eckberg, D. L., & Ebert, T. J. (1983). Muscarinic cholinergic receptors modulate vagal cardiac responses in man. *Journal of the Autonomic Nervous System, 7*, 271–278.

Ramanathan, A., & Myers, G. A. (1995). Data preprocessing in spectral analysis of heart rate variability. *Journal of Electrocardiology, 29*, 45–47.

Randall, W. C. (1994). Efferent sympathetic innervation of the heart. In J. A. Armour & J. L. Ardell (Eds.), *Neurocardiology* (pp. 77–94). New York: Oxford University Press.

Rea, R. F., & Eckberg, D. L. (1987). Carotid baroreceptor–muscle sympathetic relation in humans. *American Journal of Physiology, 253*, R929–R934.

Richards, J. E., & Casey, B. J. (1991). Heart rate variability during attention phases in young infants. *Psychophysiology, 28*, 43–53.

Richter, D. W., & Spyer, K. M. (1990). Cardiorespiratory control. In A. D. Loewy & K. M. Spyer (Eds.), *Central regulation of autonomic functions*. (pp. 189–207). New York: Oxford University Press.

Rigel, D. F., Lipson, D., & Katona, P. G. (1984). Excess tachycardia: Heart rate after antimuscarinic agents in conscious dogs. *American Journal of Physiology, 84*, H168–H173.

Riniolo, T., & Porges, S. W.. (1997). Inferential and descriptive influences on measures of respiratory sinus arrhythmia: Sampling rate, R-wave trigger accuracy, and variance estimates. *Psychophysiology, 34*, 613–621.

Rompelman, O., Coenen, A. J. R. M., & Kitney, R. I. (1977). Measurement of heart rate variability. Part I: Comparative study of heart rate variability analysis methods. *Medical and Biological Engineering and Computing, 15*, 233–239.

Rompelman, O., Snijders, J. B. I. M., & van Spronsen, C. J. (1982). The measurement of heart rate variability spectra with the help of a personal computer. *IEEE Transactions on Biomedical Engineering, 29*, 503–510.

Rosenbaum, M., & Race, D. (1968). Frequency–response characteristics of vascular resistance vessels. *American Journal of Physiology, 215*, 1397–1402.

Rosenblueth, A., & Simeone, F. A. (1934). The interrelations of vagal and accelerator effects on the cardiac rate. *American Journal of Physiology, 110*, 42–55.

Rother, M., Witte, H., Zwiener, U., Eiselt, M., & Fischer, P. (1989). Cardiac aliasing—A possible cause for the misinterpretation of cardiorespirographic data in neonates. *Early Human Development, 20*, 1–12.

Sands, K. E. F., Appel, M. L., Lilly, L. S., Schoen, F. J., Mudge, G. H., & Cohen, R. J. (1989). Power spectral analysis of heart rate variability in human cardiac transplant recipients. *Circulation, 79*, 76–82.

Saul, J. P., Albrecht, P., Berger, R. D., Cohen, R. J. (1988). Analysis of long term heart rate variability: Methods, 1/f scaling and implications. *Computers in Cardiology, 15*, 419–422.

Saul, J. P., Arai, Y., Berger, R. D., Lilly, L. S., Colucci, W. S., & Cohen, R. J. (1988). Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. *American Journal of Cardiology, 61*, 1292–1299.

Saul, J. P., Berger, R. D., Albrecht, P., Stein, S. P., Chen, M. H., & Cohen, R. J. (1991). Transfer function analysis of the circulation: Unique insights into cardiovascular regulation. *American Journal of Physiology, 261*, H1231–H1245.

Saul, J. P., Berger, R. D., Chen, M. H., & Cohen, R. J. (1989). Transfer function analysis of autonomic regulation: II. Respiratory sinus arrhythmia. *American Journal of Physiology, 256*, H153–H161.

Saul, J. P., Kaplan, D. T., & Kitney, R. I. (1988). Nonlinear interactions between respiration and heart rate: A phenomenon common to multiple physiologic states. *Computers in Cardiology, 15*, 299–302.

Saul, J. P., Parati, G., Cohen, R. J., & Lam, K. H. (1992). Identification of dynamic baroreflex responses using random interval neck stimulation [Abstract]. *Circulation, 86*, I-481.

Saul, J. P., Rea, R. F., Eckberg, D. L., Berger, R. D., & Cohen, R. J. (1990). Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity. *American Journal of Physiology, 258*, H713–H721.

Sayers, B. McA. (1973). Analysis of heart rate variability. *Ergonomics, 16*, 17–32.

Scheffer, G. J., TenVoorde, B. J., Karemaker, J. M., & Ros, H. H. (1994). Effects of epidural analgesia and atropine on heart rate and blood pressure variability: Implications for the interpretation of beat-to-beat fluctuations. *European Journal of Anaesthesiology, 11*, 75–80.

Shapiro, P. A., Sloan, R. P., Bagiella, E., Bigger, J. T., & Gorman, J. M. (1996). Heart rate reactivity and heart period variability throughout the first year after heart transplantation. *Psychophysiology, 33*, 54–62.

Sheffield, L. T., Berson, A., Bragg-Remschel, D., Gillette, P. C., Hermes, R. E., Hinkle, L., Kennedy, H., Mirvis, D. M., & Oliver, C. (1985). AHA special report. Recommendations for standards of instrumentation and practice in the use of ambulatory electrocardiology. Task force of the Committee on Electrocardiology and Cardiac Electrophysiology of the Council on Clinical Cardiology. *Circulation, 71*, 626–636A.

Shine, J., Potter, E. K., Biden, T., Selbie, L. A., & Herzog, H. (1994). Neuropeptide Y and regulation of the cardiovascular system. *Journal of Hypertension, 12*(Suppl.), S41–S45.

Siegel, G. (1983). Principles of vascular rhythmogenesis. *Progress in Applied Microcirculation, 3*, 40–62.

Sleight, P., La Rovere, M. T., Mortara, A., Pinna, G., Maestri, R., Leuzzi, S., Bianchini, B., Tavazzi, L., & Bernardi, L. (1995). Physiology and pathophysiology of heart rate and blood pressure variability in humans: Is power spectral analysis largely an index of baroreflex gain? *Clinical Science, 88*, 103–109.

Sloan, R. P., Shapiro, P. A., Bagiella, E., Bigger, J. T., Jr., Lo, E. S., & Gorman, J. M. (1996). Relationships between circulating catecholamines and low frequency heart period variability as indices of cardiac sympathetic activity during mental stress. *Psychosomatic Medicine, 58*, 25–31.

Sloan, R. P., Shapiro, P. A., Bagiella, E., Gorman, J. M., & Bigger, J. T., Jr. (1995). Temporal stability of heart period variability during a resting baseline and in response to a psychological challenge. *Psychophysiology, 32*, 191–196.

Somsen, R. J. M., Molenaar, P. C. M., van der Molen, M. W., & Jennings, J. R. (1991). Behavioral modulation patterns fit an animal model of vagus–cardiac pacemaker interactions. *Psychophysiology, 28*, 383–399.

Spear, J. F., Kronhaus, K. D., Moore, E. N., & Kline, R. P. (1979). The effect of brief vagal stimulation on the isolated rabbit sinus node. *Circulation Research, 44*, 75–88.

Stephensen, R. B., Smith, O. A., & Scher, A. M. (1981). Baroreflex regulation of heart rate in baboons during different behavioral states. *American Journal of Physiology, 241*, 277–285.

Steptoe, A., & Sawada, Y. (1989). Assessment of baroreceptor reflex function during mental stress and relaxation. *Psychophysiology, 26*, 140–147.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation, 93*, 1043–1065.

Taylor, J. A., Carr, D. L., & Eckberg, D. L. (1997). *Mechanisms underlying*

very low frequency R–R interval oscillations in humans. Manuscript submitted for publication.

Thackray, R. I., Jones, K. N., & Touchstone, R. M. S. (1974). Personality and physiological correlates depend on a monotonous task requiring sustained attention. *British Journal of Psychology, 65*, 351–358.

Thorne, P. R., Engel, B. T., & Holmblad, J. B. (1976). An analysis of the error inherent in estimating heart rate from cardiotachometer records. *Psychophysiology, 13*, 269–272.

Ulman, L. G., Moriarity, M., Potter, E. K., & McCloskey, D. I. (1993). Galanin antagonist effects on cardiac vagal inhibitory actions of sympathetic stimulation in anaesthetized cats and dogs. *Journal of Physiology, 464*, 491–499.

van den Aardweg, J. G., & Karemaker, J. M. (1991). Respiratory variability and associated cardiovascular changes in adults at rest. *Clinical Physiology, 11*, 95–118.

van Steenis, H. G., Tulen, J. H., & Mulder, L. J. (1994). Heart rate variability spectra based on non-equidistant sampling: The spectrum of counts and the instantaneous heart rate spectrum. *Medical Engineering and Physics, 16*, 355–362.

Wallin, B. G., Esler, M., Dorward, P., Eisenhofer, G., Ferrier, C., Westerman, R., & Jennings, G. (1992). Simultaneous measurements of cardiac noradrenaline spillover and sympathetic outflow to skeletal muscle in humans. *Journal of Physiology, 453*, 45–58.

Watkins, L., Grossman, P., & Sherwood, A. (1996). Noninvasive assessment of baroreflex control in borderline hypertension: Comparison with the phenylephrine method. *Hypertension, 28*, 238–243.

Weber, E. J., Molenaar, P. C., & van der Molen, M. W. (1992a). A nonstationarity test for the spectral analysis of physiological time series with an application to respiratory sinus arrhythmia. *Psychophysiology, 29*, 55–65.

Weber, E. M. J., Molenaar, P. C. M., & van der Molen, M. W. (1992b). On spectral analysis and nonstationarity: Why not use a test if one is available? *Psychophysiology, 29*, 73–75.

Weber, R. J. M., van der Molen, M. W., & Molenaar, P. C. M. (1994). Heart rate and sustained attention during childhood: Age-changes in anticipatory heart rate, primary bradycardia, and respiratory sinus arrhythmia. *Psychophysiology, 31*, 164–174.

West, N. H., & van Vliet, B. N. (1983). Open-loop analysis of the pulmocutaneous baroreflex in the toad Bufo marinus. *American Journal of Physiology, 245*, R642–R650.

Witte, H., Zwiener, U., Rother, M., & Glaser, S. (1988). Evidence of a previously undescribed form of respiratory sinus arrhythmia (RSA)—The physiological manifestation of "cardiac aliasing." *Pflugers Archives—European Journal of Physiology, 412*, 442–444.

Wolf, S. (1967). The end of the rope: The role of the brain in cardiac death. *Canadian Medical Association Journal, 97*, 1022–1025.

Wundt, W. (1902). *Grundzüge der physiologischen Psychologie* (Vol. 2). Leipzig: W. Engelmann.

Xia, R., Odemuyiwa, O., Gill, J., Malik, M., & Camm, A. J. (1993). Influence of recognition errors of computerised analysis of 24-hour electrocardiograms on the measurement of spectral components of heart rate variability. *International Journal of Biomedical Computing, 32*, 223–235.

Yang, T., Senturia, J. B., & Levy, M. N. (1994). Antecedent sympathetic stimulation alters time course of chronotropic response to vagal stimulation in dogs. *American Journal of Physiology, 266*, H1339–H1347.

Zweibel, S. L., Bloomfield, D. M., & Bigger, J. T. (1995). RR variability detects increases in vagal modulation with phenylephrine infusion. *Circulation, 92*(Suppl.), I-144.

Zwiener, U., Luthke, B., Bauer, R., Richter, A., Hoyer, D., & Wagner, H. (1994). Forms of physiological aliasing within the heart rate fluctuations by higher frequent respiratory movements. *Journal of Physiology and Pharmacology, 45*, 563–572.

(RECEIVED February 24, 1997; ACCEPTED April 22, 1997)