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The metrics of cardiac chronotropism: Biometric perspectives

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Abstract

The selection of heart period versus heart rate as a chronotropic metric has been considered from quantitative and statistical perspectives, which have not yielded a universal preference for either metric. In the present paper, we discuss biometric considerations that bear on the selection of the optimal chronotropic metric. Biometric evidence reveals that the transfer functions relating autonomic nerve traffic to chronotropic effects on the heart are more nearly linear for heart period than for heart rate. This confers considerable advantage on heart period as a chronotropic metric and can facilitate the study of psychophysiological relationships. We further show that heart period offers greater flexibility, because heart period data can be evaluated in cardiac time units (beats) or in real-time units (s), whereas heart rate data can only be analyzed in real time. These considerations suggest clear advantages to heart period as a chronotropic metric.

Descriptors: Autonomic nervous system, Heart period, Heart rate, Law of initial values, Baseline dependency, Chronotropic metrics

Considerable discussion has arisen in the psychophysiological literature concerning the selection of heart period versus heart rate as the appropriate chronotropic metric (Graham, 1978a, 1978b; Graham & Jackson, 1970; Jennings, Stringfellow, & Graham, 1974; Khachaturian, Kerr, Kruger, & Schachter, 1972; Richards, 1980). This debate has largely revolved around statistical issues related to the normality and homogeneity of variance of heart period and heart rate distributions, and the appropriate time base for these alternate metrics. Although no universal consensus has been reached on this issue, some general perspectives have emerged from the earlier literature. First, although both heart rate and heart period distributions frequently deviate from the normal distribution, these deviations are not generally severe, and differences across individuals or ages are often considerably larger than differences between the metrics (Graham, 1978b). On distributional grounds, neither heart rate nor heart period appear to be clearly superior in adult subjects, although heart rate may have a slight advantage in infants (Graham, 1978b). Finally, it has been argued that heart rate is the most appropriate metric for real-time analyses, whereas heart period is the natural metric for analysis in cardiac time (Graham, 1978b). In summary, neither statistical nor distributional characteristics allow a universal and unambiguous selection among period and rate metrics of chronotropism.

In contrast, the thesis of the present paper is that biometric issues, which have received relatively little attention in the historical literature, offer a strong set of criteria for selection of heart period over heart rate as a chronotropic metric.

Psychophysiological relationships entail two classes of transformations[1]: (a) from psychological antecedents to autonomic outflows and (b) from autonomic outflows to functional effects on visceral organs. Although each of these classes of transformation is important in its own right, psychophysiologists are generally more interested in the former set of transforms rather than the peripheral autonomic physiology per se. Each of these sets of transformations, however, impacts on the empirical results of psychophysiological studies because the effects of psychological antecedents are measured in terms of visceral response rather than autonomic outflows. Consequently, any nonlinearities at peripheral levels may cloud or obscure psychophysiological relationships. It was this general recognition, for example, that led to the recommendation of skin conductance over skin resistance as a metric for electrodermal response (Dawson, Schell, & Filion, 1990; Venables & Christie, 1980). In general, it is desirable to minimize the impact of nonlinear peripheral transformations, so that psychophysiological relationships more closely reflect and illuminate behavioral or psychological processes. In

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[1] We use the term *transformation* in the general sense of a translation from a set of antecedents (e.g., perceptual processing of a stimulus) to a set of consequences (e.g., affective reaction), rather than in the more restrictive sense of a formal mathematical transform.

this regard, we show that heart period is superior to heart rate at a chronotropic metric. Although Graham (1978a) argued that the natural units for analysis of heart period are in cardiac time, and those for heart rate are in real time, we also show that heart period offers greater analytical flexibility. This is because time-weighted heart periods can also be appropriately analyzed in real time, whereas no weighting permits the proper analysis of heart rate in cardiac time.

Biometric Considerations

Psychophysiologists are generally interested in the chronotropic state of the heart as it relates to central processes associated with behavioral states or reactions. Consequently, the ideal chronotropic metric would introduce minimal nonlinearities at the peripheral level that could distort or obscure the relationship between antecedent conditions and behavioral states. In the present paper, we will show that heart period displays a more nearly linear relationship between autonomic outflows and chronotropic state than does heart rate. This is important because the inherent nonlinearities between heart rate and autonomic traffic can introduce apparent baseline dependencies and interactions that can distort or obscure psychophysiological relationships.

Autonomic-Chronotropic Transfer Functions

Direct stimulation of autonomic cardiac nerves. In a series of classic studies, Rosenblueth and colleagues provided early evidence on the quantitative relationships between autonomic activity and chronotropic effects on the heart. By direct stimulation of parasympathetic cardiac nerves in the cat, these researchers documented a consistent inverse hyperbolic relationship between evoked vagal activity and heart rate (Rosenblueth, 1932; Rosenblueth & Simeone, 1934). Representative results are illustrated in Figure 1 (upper left), which depicts the chronotropic effects of vagal stimulation over a wide range of frequencies. As is apparent, higher stimulation frequencies yield a progressively diminished effect on heart rate. This curvilinearity has since become a standard finding, although some have suggested that the relationship may be more closely approximated by parabolic or exponential functions (Levy & Zieske, 1969; Versprille & Wise, 1971).

Parker, Cellar, Potter, and McCloskey (1984) appropriately pointed out that the hyperbolic relationship between vagal activity and heart rate would necessarily be linearized if expressed in the metric of heart period. This is illustrated in Figure 1 (upper middle), which depicts the Rosenblueth and Simeone (1934) data

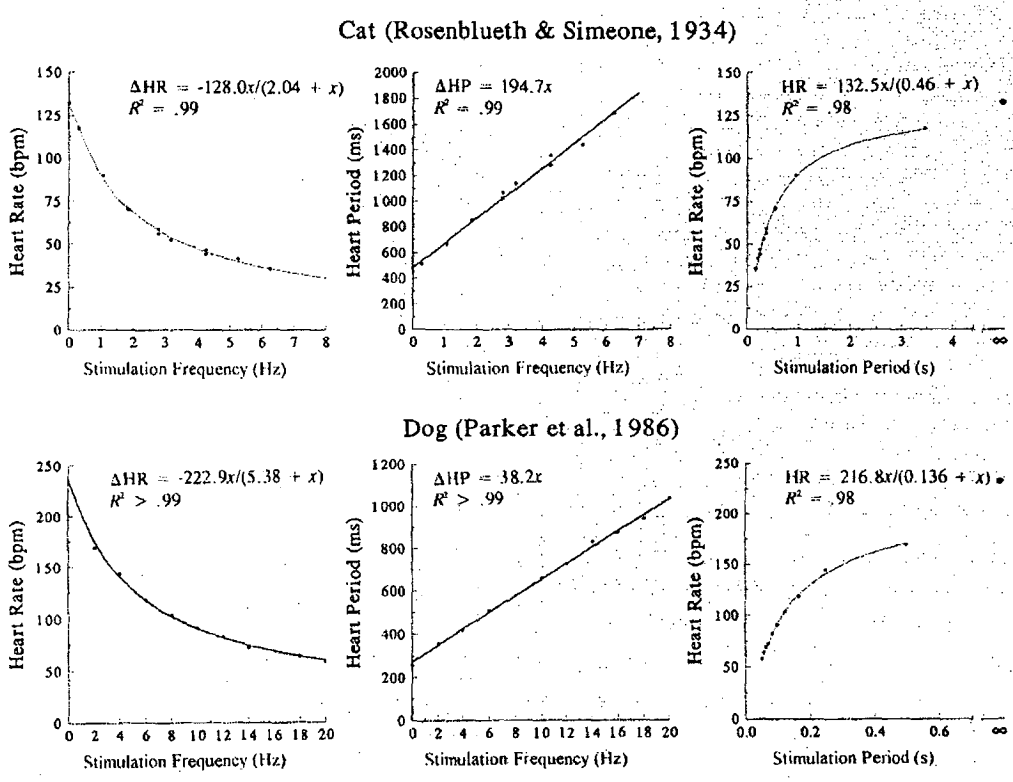


Figure 1. Effects of vagal stimulation on the chronotropic state of the heart, expressed in different metrics. Upper panels: Data are derived from Rosenblueth and Simeone (1934, Figure 1) on the chronotropic effects of vagal stimulation in the cat. Left: Heart rate (HR) as a function of vagal stimulation frequency. Middle: Heart period (HP) as a function of vagal stimulation frequency. Right: Heart rate as a function of vagal stimulation period. The large dot indicates the heart rate in the absence of stimulation. Lower panels: Data are derived from Parker, Celler, Potter, and McCloskey (1984) on the chronotropic effects of vagal stimulation in the dog. Left: Heart rate as a function of vagal stimulation frequency. Middle: Heart period as a function of vagal stimulation frequency. Right: Heart rate as a function of stimulation period. Equations in each panel express the chronotropic changes with frequency of stimulation. The large dot indicates heart rate in the absence of stimulation. (All functions are best-fit hyperbolic or linear functions).

transformed into heart period. The obverse also obtains. Parker et al. (1984) examined the effects of vagal stimulation on heart period in the dog. Their results are illustrated in Figure 1 (lower middle), and the transformation of these data into heart rate is depicted in Figure 1 (lower left).

This consideration is based on the expression of stimulation in terms of frequency. This is the typical and natural metric for neural activity, as synaptic events are transient and it is generally the temporal density of these synaptic events that determine an effector response. It is important to note, however, that the relationship between heart rate and nerve activity can not be linearized by merely changing the scaling of the abscissa from stimulation frequency to stimulation period (see Figure 1, right panels). Although it is also the case that heart period is nonlinearly related to stimulation period, the point is that heart period does show a relative linearity to vagal activity when the latter is expressed in the appropriate frequency metric. The fact that heart period rather than heart rate assumes this linearity is related to the functional translation that occurs at the sinoatrial synapse.

The functional basis of the observed linearity between vagal activity and heart period is clarified by the model of Dexter, Levy, and Rudy (1989) for vagal control of the heart. This biophysical model is based on empirically derived estimates of the release, accumulation, and chronotropic effects of acetylcholine at vagal cardiac synapses of the sinoatrial node. Based on the quantitative dynamics of these processes, the Dexter et al. (1989) model permits an estimate of the relationship between vagal activation frequency and the chronotropic state of the heart. The predicted function for the dog is illustrated in Figure 2. The linearity of the predicted function relating vagal activity to chronotropic state arises as a consequence of two nonlinear processes: (a) a negatively accelerating function relating vagal frequency to acetylcholine concentrations at sinoatrial synapses and (b) a positively accelerating function relating acetylcholine concentration to heart period.

The linearity between vagal frequency and heart period is not limited to dogs and cats but appears to be a general feature of vagal control of the heart in mammals. An essentially linear relationship between vagal stimulation frequency and heart period has also been reported for the rat (Berntson, Quigley, Fabro, & Cacioppo, 1992) and the rabbit (Versprille & Wise, 1971). Moreover, although human stimulation studies are limited, the existing data also suggest a similar linearity in the vagal control of the human heart. The relation between the frequency of parasympathetic cardiac nerve stimulation and chronotropic state in humans has been reported to be approximately hyperbolic when expressed in heart rate (Carlsten, Folkow, & Hamberger, 1957) and appears to be essentially linear when expressed in heart period[2] (Carlson et al., 1992).

Interpretation of the results of sympathetic cardiac nerve stimulation is somewhat more problematic than for the parasympathetic system. First, the potent blood pressure responses generally produced by sympathetic stimulation can lead to striking increases in parasympathetic outflow, which can reflexively

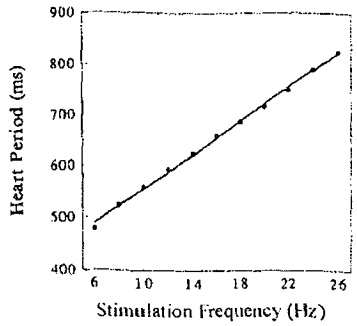


Figure 2. Predicted function relating vagal stimulation frequency and heart period, as derived by Dexter, Levy, and Rudy (1989). Predicted data points were derived from a quantitative physiological model of the release, accumulation, and chronotropic effects of acetylcholine at vagal cardiac synapses of the sinoatrial node.

dampen sympathetically mediated alterations in cardiac chronotropy (e.g., Vassalle, Levine, & Stuckey, 1968). Although indirect reflex effects must always be addressed in stimulation studies, they are particularly critical for sympathetic stimulation because of these potent pressor actions. Second, in contrast to the wide dynamic range of the parasympathetic system, sympathetic chronotropic control is modest, with a clear asymptotic limit. That limit introduces a necessary nonlinearity in the functions relating chronotropic state to stimulation frequency. In fact, sympathetic stimulation begins to approach asymptotic effects with frequencies as low as 2 Hz, and few studies have employed sufficiently fine-grained frequency variations to explore the shape of the transfer function over the normal physiological range of control. One exception is the recent study of Berger, Saul, and Cohen (1989) in the dog. The possibility of reflex confounds was eliminated by functionally isolating the heart from central control. Results of this study are illustrated in Figure 3 (left). As is apparent, the relationship between stimulation frequency and heart period closely approximates the linear, at least over the range of frequencies tested.

Because of clear asymptotic limits to sympathetic effects, nonlinearities are inevitable as these limits are approached. Indeed, some degree of nonlinearity is generally seen in sympathetic stimulation studies, over a broader range of frequencies. This is apparent in the classic study of Levy and Zieske (1969) in the dog, in which best-fit polynomial functions were derived by relating autonomic stimulation frequencies to heart rate. Although nonlinearities are apparent in these functions, the coefficients for higher-order polynomial components are modest, and a linear function provides a relatively good fit to the data. This is illustrated in Figure 3 (right), together with heart period transforms of the heart rate functions. Because of the relatively small dynamic range of sympathetic control, both heart rate and heart period functions could be closely approximated by linear functions. The linear functions accounted for 99% of the variance in heart rate and 97% of the variance in heart period. Thus, for sympathetic chronotropic control, the selection of either heart rate or heart period as a metric would not appear to introduce serious biometric biases in psychophysiological analyses as long as levels of parasympathetic control remain relatively constant across time or conditions. When chronotropic state is expressed in heart rate, however, even sympathetic effects can

[2] A threshold for chronotropic effects was apparent at low frequencies, chronotropic effects plateaued at high frequencies, and sinus arrest was observed in 2 of the 13 subjects at higher levels of stimulation. An essentially linear relationship was apparent between stimulation frequency and heart period, however, within the frequency-dependent range.

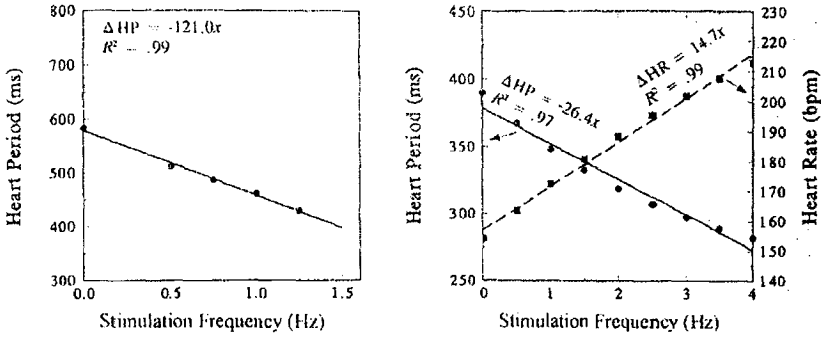


Figure 3. Sympathetic stimulation and cardiac chronotropy. Left: Relationship between the frequency of sympathetic stimulation and heart period (HP) in the dog. Data are from Berger, Saul, and Cohen (1989). Right: Functions relating sympathetic stimulation frequency to chronotropic state of the heart, expressed in heart rate (HR) and heart period. Data points were derived from the equation of Levy and Zieske (1969) ($\Delta HR = 19.64\,s - 17.95\,v - 1.225\,s^2 + 1.357\,v^2 - 1.523\,sv$), where s and v represent the sympathetic and parasympathetic stimulation frequencies. The s parameter varied between 0 and 4 Hz (the limits of sympathetic stimulation frequencies in this study), and v was set to 0. Although both heart rate and heart period data evidence nonlinearities, both data sets are closely approximated by linear functions.

be severely distorted by level shifts associated with parasympathetic actions. We will consider this issue in detail below.

Neurophysiological recording of autonomic activity in cardiac nerves. Direct electrical activation of autonomic nerves reveals that heart period displays a greater overall linearity with the frequency of nerve stimulation than does heart rate. Although potential reflex biases in these studies were generally precluded by decentralization, stimulation can not be expected to yield the normal spatiotemporal patterning characteristic of endogenous activity. Direct recordings of endogenous autonomic activity, however, have provided converging evidence on the linearity between heart period and autonomic nerve traffic. An approximate linearity between vagal firing rate and heart period has been demonstrated over variations in endogenous vagal activity associated with both respiration (Jewett, 1964; Katona, Poitras, Barnett, & Terry, 1970; Koizumi, Terui, & Kollai, 1985; Lumbers, McCloskey, & Potter, 1979) and baroreceptor activation induced either mechanically or pharmacologically (Katona et al., 1970; Koizumi et al., 1985). Importantly, this linearity was apparent over a wide range of vagal activity and heart period levels (e.g., changes in heart period >500 ms, or 160 bpm; Lumbers et al., 1979). Moreover, the Koizumi et al. (1985) study suggests that the linearity between autonomic outflows and heart period characterizes sympathetic as well as parasympathetic cardiac nerves. These results are illustrated in Figure 4, which shows the relations between variations in heart period and the endogenous activities of sympathetic and parasympathetic nerves during slow spontaneous fluctuations of heart period and blood pressure.

Summary and implications. The studies just discussed document a more nearly linear relationship between autonomic outflows and heart period than for heart rate. Indeed, with heart period as the metric, the linear components of the functions relating autonomic activities to chronotropic state account for the vast proportion of the variance. In the earlier examples, nerve stimulation and endogenous nerve activity were expressed in frequency units (Hz). This is a natural metric for expressing neurophysiological unit activity because, for example, doubling (or halving) the frequency reflects a doubling (or halving) of nerve activity. This correspondence would not hold if nerve activity were expressed as period. Nevertheless, the relationship between heart rate and nerve activity might assume linearity if nerve stimulation or activity were expressed in a period metric. In fact, Figure 1 (left panels) illustrates that this is not the case. Heart rate evidences a nonlinear relationship to autonomic nerve activity, regardless of the metric within which the nerve activity is expressed. Thus, when chronotropic state is expressed in heart rate, autonomic-effector transfer functions can introduce substantial nonlinear distortions into psychophysiological relationships. We now turn to this issue.

Consequences of Nonlinearities for Psychophysiology

Statistical and distributional characteristics of heart rate and heart period do not permit a definitive selection between these metrics. Moreover, because heart rate and heart period are mutual reciprocals, there is a fundamental symmetry in the quantitative consequences of these reciprocal transforms. These consequences are illustrated by the classic problem of baseline dependency in psychophysiology.

The dependency of phasic response on baseline functional state has been a traditional problem in psychophysiology (Lacey & Lacey, 1962; Wilder, 1957, 1967). Perhaps the most widely recognized "law" in psychophysiology is the law of initial val-

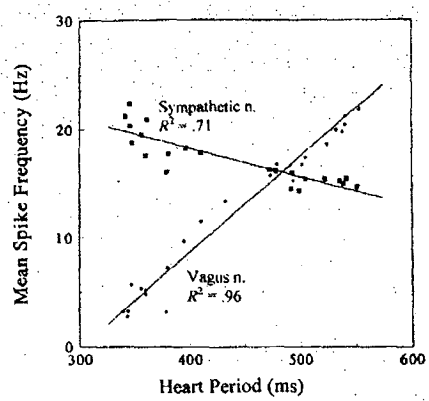


Figure 4. Relationship between spontaneous fluctuations in heart period and neurophysiologically recorded activity in autonomic cardiac nerves. Results are derived from Koizumi, Terui, and Kollai (1985). Each data point represents the average over 20 heart cycles.

ues (LIV), which was formulated to account for response variance attributable to baseline levels. In Wilder's (1957, 1967) formulation, the LIV asserts that at higher initial baseline levels, incremental responses to function-raising stimuli tend to be smaller, and decremental responses to function-depressing stimuli tend to be larger (and vice versa at lower baseline levels). A systematic change in the magnitude of response as a function of baseline level introduces added complexity and potential biases in psychophysiological analyses. On the one hand, to the extent that baseline dependencies arise from the functional organization of central behavioral–autonomic systems, they constitute inherent aspects of psychophysiological relationships that warrant study. On the other hand, apparent baseline dependencies introduced as artifacts of the metric one selects can obscure lawful relationships and lead to erroneous interpretations. Thus, a response of fixed heart period magnitude that is independent of baseline will evidence an apparent baseline dependency when expressed in heart rate. Symmetrically, a baseline-independent heart rate response will display a baseline dependency when expressed in heart period.

Biometrics and the reciprocal symmetry. Because of the symmetry in the consequences of reciprocal transforms, an obvious question arises as to whether heart rate or heart period affords a more felicitous metric for psychophysiological studies. The biometric issues raised earlier, however, address this question. As long as asymptotic limits are not approached, the essential linearity between autonomic outflows and heart period implies that autonomic-effector transform functions, per se, would neither impose nor obscure a correlation between the amplitude of an autonomic response and the autonomic baseline. In contrast, the nonlinear transformation of heart period into heart rate can be mathematically biased toward a correlation between basal state and phasic response, even when no such correlation exists in autonomic control mechanisms.[3]

Although potential biases associated with the use of heart rate may have modest consequences for some types of questions, as heart rate and heart period are monotonically related, they can seriously distort other psychophysiological analyses. The interpretive errors that can be introduced by spurious baseline dependencies are illustrated by a recent study of the contributions of the autonomic branches to the chronotropic response to orthostatic and psychological stressors (Berntson, Cacioppo, & Quigley, 1994; Cacioppo et al., 1994). Baroreflex responses associated with the assumption of a standing posture yield reciprocal increases in sympathetic, and decreases in parasympathetic, control of the heart (Berntson, Cacioppo, & Quigley, 1993b; Head & McCarty, 1987; Spyer, 1990). By selective blockades of the autonomic branches, pharmacological antagonists can provide quantitative estimates of the independent contributions of the branches to the chronotropic response (Berntson et al., 1994; Stemmler, 1993; Stemmler, Grossman, Schmid, & Foerster, 1991). Based on an analysis of heart periods during pharmacological blockades, we found a significant level of tonic sympathetic control of cardiac chronotropy, and an even greater level of parasympathetic tone, under basal sitting conditions (Cacioppo et al., 1994). In accord with the known physiology of orthostatic stress, pharmacological blockades also revealed that the decrease in heart period associated with standing was attributable to a significant increase in sympathetic control (−19 ms), and an even larger reciprocal decrease in parasympathetic control (−84 ms). The decrease in parasympathetic tone during standing was also indicated by the significant decrease in the magnitude of respiratory sinus arrhythmia, a noninvasive index of parasympathetic control of the heart (e.g., see Berntson, Cacioppo, & Quigley, 1993a, Porges, 1986).

When these data were transformed into heart rate, however, analyses of pharmacological blockades suggested a minimal and nonsignificant parasympathetic contribution to the response to orthostatic stress. This was due to the large basal shifts in chronotropic levels produced by pharmacological blockades, together with the associated biases introduced by the nonlinearities inherent in heart rate–autonomic relationships. These biases are illustrated by the effects of parasympathetic blockade with atropine. In the unblocked condition, the heart rate increase associated with standing was approximately 16 bpm (from a baseline of ≈ 72 bpm). By blocking the parasympathetic contribution, atropine should allow an evaluation of the independent, residual contribution of the unblocked sympathetic branch. After atropine, however, standing continued to yield an approximately 16-bpm heart rate increase. This suggested that increased sympathetic activity alone accounted for the heart rate effect, with minimal contribution from the parasympathetic system.

This interpretation is confounded, however, by the large baseline shift in heart rate produced by atropine (from 72 to 117 bpm). The comparable heart rate responses to orthostatic challenge, under atropine, are attributable to this large increase in baseline levels, together with the nonlinear heart rate transform that exaggerates responses at high basal levels. Fortunately, this confound was detectable by a recently developed validity index for blockade analyses, which captures potential biases in blockade studies, including those associated with nonlinearities in psychophysiological response functions (Berntson et al., 1994). This validity metric revealed that the estimate of parasympathetic control derived from heart rate had low validity, whereas the comparable analysis of heart period yielded valid estimates (see Cacioppo et al., 1994). In this case, inappropriate interpretations based on heart rate data were precluded by the availability of a validity statistic in the Cacioppo et al. (1994) blockade study. In many cases, however, potential biases from the nonlinearities in the autonomic–heart rate relationship may go undetected.

Another example derives from the literature on autonomic interactions. Mutual inhibitory interactions among the autonomic branches, for example, have been documented in the autonomic control of the heart (Hall & Potter, 1990; Levy, 1984; Levy & Zieske, 1969; Manabe et al., 1991). These interactions complicate the estimation of the independent contributions of the autonomic branches to psychophysiological response. Although true interactions should not be disregarded, their mag-

[3] Rate measures compress data at lower heart rate levels (longer heart periods) and expand values at faster heart rates (shorter heart periods). This selective compression/expansion of chronotropic values introduces a differential bias related to the direction of phasic response. Transforms of fixed incremental heart period responses into heart rate yield an apparent baseline dependency in accord with the law of initial values (LIV). The resulting heart rate decrements become larger at higher basal levels and smaller at lower levels. The transformation of equivalent decremental heart period responses into heart rate, in contrast, leads to an apparent baseline dependency that is contrary to the LIV. In this case, resulting heart rate increases become larger at higher basal levels and smaller at lower basal levels. Thus, heart rate measures can either exaggerate or oppose physiological baseline dependencies, depending on the direction of the phasic response.

nitude, and hence their impact on psychophysiological analyses, may be exaggerated by the use of heart rate (Quigley & Berntson, 1994). Indeed, the inherent nonlinearities between autonomic nerve traffic and heart rate can appear as "interactions" among the autonomic branches, even when no functional interaction exists. Given a general linear model between autonomic outflows and heart period, the dynamic range of the sympathetic branch, for example, is equivalent at varied levels of parasympathetic control (and thus basal heart period). When expressed in heart rate, however, the dynamic range of the sympathetic branch varies considerably as a function of the parasympathetic level, being maximal at low parasympathetic levels and negligible at the highest levels of parasympathetic tone. That is, the functional consequences of sympathetic activity now appear to interact with vagal control.

A recent study of autonomic interactions in chronotropic control, under relatively naturalistic conditions, is particularly illuminating (Stramba-Badiale et al., 1991). Chronic vagal stimulation electrodes were surgically implanted in dogs, and the animals were allowed to recover from anesthesia prior to testing. Sympathetic activation was then induced by exercise, while varied levels of vagal stimulation were delivered. Results, reported in both heart rate and heart period, revealed significant autonomic "interactions" only when the chronotropic state was expressed in heart rate. In a recent analysis of the interaction literature, Quigley and Berntson (1994) documented (a) that autonomic interactions are generally exaggerated when expressed in heart rate, and (b) when expressed in heart period, residual interactions are largely limited to the extremes of autonomic activation. Autonomic interactions constitute an integral and important aspect of autonomic control, and should not be disregarded. At the same time, however, the magnitude of these interactions can be exaggerated, and spurious interactions introduced by the use of heart rate. This imposes an unnecessary complexity in psychophysiological analyses.

Summary and implications. The findings and considerations just outlined indicate that the use of heart rate as a chronotropic metric can bias estimates of baseline dependency and autonomic interactions in psychophysiological studies. Indeed, apparent baseline dependencies and autonomic interactions can be spuriously introduced by nonlinear heart rate transforms. If not recognized, these transformational artifacts can complicate interpretations of chronotropic response and lead to erroneous conclusions concerning psychophysiological relationships. Although both baseline dependencies and autonomic interactions may in fact influence psychophysiological measures, attempts to identify and quantify these phenomena could be appreciably facilitated by the use of heart period as the chronotropic metric. In addition, the use of heart period can greatly facilitate interpretations of pharmacological blockades, as the nonlinearities in heart rate can appear as biases in validity estimates derived from blockade studies (Berntson et al., 1994).

The Time Base Issue

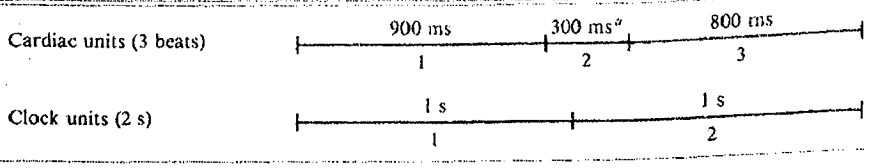
Graham (1978b) raised an issue as to the appropriate time base (real time vs. cardiac time) for the alternate metrics of heart rate versus heart period. This is an important issue because it may set analytical constraints on the use of heart period and heart rate metrics. Graham argued that heart rate is the appropriate metric for real-time (second by second) analyses, whereas heart period is more appropriate for analyses in cardiac time (beat by beat). The argument is based on the fact that for unbiased estimates the average value across subsets of data will equal the overall average. Graham illustrated the problem with the example shown in Table 1, where three beats occur within the span of 2 s. This yields an overall heart rate of 90 bpm (3 beats/2 s = 1.5 beats/s * 60 = 90 bpm), and a mean heart period of 0.667 s or 667 ms (2 s/3 beats = 0.667 s/beat or 667 ms/beat). When the unit of analysis is cardiac time (beats), the average of the individual heart periods yields an unbiased estimate of the overall heart period ([900 + 300 + 800 ms]/3 = 667 ms), whereas the average of the beat-by-beat heart rates does not equal the overall heart rate (113.89 vs. 90 bpm, Table 1). In contrast, when the unit of analysis is real time (s), the average of the second-by-second heart rate values now provides an unbiased estimate of the overall heart rate ([80 + 100]/2 = 90 bpm), but the average of the second-by-second heart period values does not equal the overall heart period (675 vs. 667 ms, Table 1). This is a crucial issue because common statistical analyses assume the use of unbiased estimates. In fact, when chronotropic state is a repeated-measures factor, main effects are derived from the average across the repeated measures. Because of the potential biases in estimates of central tendency for heart period expressed in real time, and for heart rate expressed in cardiac time, Graham (1978b) recommended that heart period be used for analyses in cardiac-time and heart rate for real-time analyses.

The quantitative bases for the recommendation of Graham (1978b) are relatively straightforward. When heart periods (with dimensions of s/beat) are analyzed in units of cardiac time, the heart period values are appropriately scaled in the basic unit of analysis (i.e., beats). Because of the common denominator, heart period values can be aggregated across subsets of beats, and the mean of these subsets will yield the overall average heart period across all beats (see Table 1). In contrast, the basic unit for real-time analyses is seconds, whereas the heart period values are scaled in units of beats (ms/beat). Because beats vary in duration, when heart periods are aggregated over time, they do not have a common denominator consistent with the unit of analysis (s). Hence, as illustrated in Table 1, the average of the mean heart period across seconds may not equal the overall heart period averaged across all beats.

Similarly, when heart rate in beats/s is analyzed in real time, the heart rate values are appropriately scaled and expressed in the basic unit of analysis (i.e., s). Again, because of the common denominator, heart rate values can be aggregated across subsets of time (s), and the mean of these resulting subsets will yield the overall average heart period across all intervals (see Table 1). When analyzed in cardiac units, however, the time scaling of heart rate (beats/s) is not consistent with the unit of analysis (beats). Because interbeat intervals may differ, when heart rate values are aggregated across beats, they are not appropriately scaled by the respective durations of those beats. Consequently, the average heart rate values for individual beats may not equal the overall heart rate averaged across all beats.

Heart period. The problem can be further illustrated by considering the analysis of heart period in real time. Because beats differ in duration, individual heart periods (in ms/beat) are not evenly scaled in the units of analysis (s), and when aggregated over time (as in the derivation of second-by-second means) they are not appropriately weighted by their duration. Thus, as illustrated in Table 1, the average of the mean heart period across

Table 1. *The Time Base Problem as Posed by Graham (1978b)*



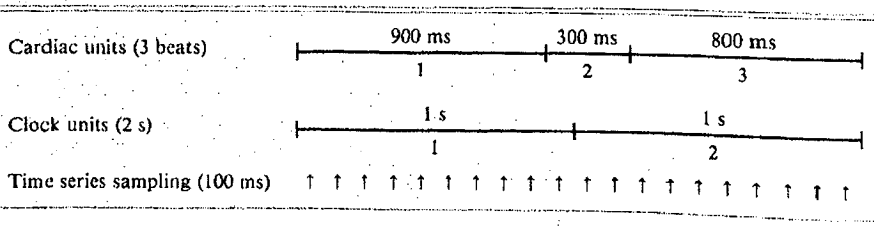
		Data format		
			Heart rate[b]	
Units of analysis (denominator)	Data subset	Heart period[b] (ms/beat)	beats/s	beats/min
Overall	3 beats in 2 s	667	1.5	90.00
Cardiac units (beats)	Beat 1	900	1.11	66.67
	Beat 2	300	3.33	200.00
	Beat 3	800	1.25	75.00
	Mean	667	1.90	113.89
Real-time units (s)	Second 1	750	1.33	80.00
	Second 2	600	1.67	100.00
	Mean	675	1.50	90.00

[a]Although this heart period would generally be considered to be out of the physiological range, we employ this value so as to be consistent with the example of Graham (1978b). [b]For beats that cross second boundaries, the individual heart rate and heart period estimates are based on the proportion of the beat falling within the relevant 1-s interval.

seconds may not equal the overall heart period averaged across all beats. This, as Graham (1978b) pointed out, violates the definitional requirement of an arithmetic mean. In short, the method employed by Graham for deriving mean heart period over time, which is commonly employed in the literature, does not yield heart period estimates that are appropriate for real-time analyses.

This limitation, however, is related to the manner by which mean heart periods are estimated and should not lead to a general proscription of the analysis of heart period data in real-time units. The primary interest in real-time analyses is the estimation of chronotropic levels at given points in time, or in the temporal structure of chronotropic changes. Consequently, the unweighted averaging of heart periods over time does not appropriately scale the individual beats by the relative proportion of the temporal interval that they occupy (Cheung & Porges, 1977; De Boer, Karemaker, & Strackee, 1985; Porges & Byrne, 1992). This is further illustrated in Table 2, by a time-sampling approach to estimating mean heart period, which is similar to the approach of Cheung and Porges (1977) and De Boer et al.

Table 2. *Analyzing Heart Period Data in Cardiac and Real Time*



Units of analysis (denominator)	Data subset	Heart period (ms/beat)	Weighted heart period* (ms/beat)
Overall	3 beats in 2 s	667	770
Cardiac units (beats)	Beat 1	900	900
	Beat 2	300	300
	Beat 3	800	800
	Mean	667	667
Real-time units (s)	Second 1	750	840
	Second 2	600	700
	Mean	675	770

*Weighted heart period is the sum of the products of the individual beats and their durations, divided by the overall interval (in seconds).

(1985). Table 2 depicts the heart period values of Table 1, together with a time series (arrows) for the estimation of the instantaneous heart period at 100-ms intervals. For the overall 2-s epoch, this time series estimation would yield 9 samples at 900 ms for the first beat, 3 samples at 300 ms for the second beat, and 8 samples at 800 ms for the last beat. This approach appropriately weights the individual beats by the proportion of the (2-s) analytical epoch that they occupy, and yields a time-weighted estimate of the heart period over that epoch of 770 ms. This weighted mean (mn_w) represents the sum of the individual heart periods multiplied by the proportion of the (2-s) interval occupied by the respective heart period (mn_w = [900 ms * 9/20] + [300 ms * 3/20] + [800 ms * 8/20] = 770 ms). This is equivalent to summing the products of the individual heart periods and their respective durations, and dividing by the number of seconds in the analysis interval (i.e., mn_w = [900 ms * 0.9 + 300 ms * 0.3 + 800 ms * 0.8]/2 s = 770 ms). Similarly, for the first second, the time series estimation would yield 9 samples at 900 ms for the first beat, and 1 sample at 300 ms for the second beat, yielding a weighted mean of 840 ms (mn_w = [900 ms * 0.9 + 300 ms * 0.1]/1 s = 840 ms). In like fashion, the weighted mean heart period for the next 1 s is 700 ms (mn_w = [300 ms * 0.2 + 800 ms * 0.8]/1 s = 700 ms).

Table 2 shows both the raw and the weighted heart period values expressed in both cardiac and real-time units. When expressed in units of cardiac time, the average of the beat-by-beat heart periods equals the overall average, whereas this identity does not hold for real-time units. That is, raw heart period values provide an unbiased estimate of the overall mean, and thus conform with definitional requirements only when expressed in units of cardiac time. For weighted heart period values, however, the second-by-second (real-time) means now equal the overall weighted mean based on all heart periods, whereas the beat-by-beat (cardiac-time) values do not. Thus, time-weighted heart periods fulfill the definitional requirements articulated by Graham, and permit analysis of heart period data in real time.

The time-weighting outlined above scales the heart period data to a common (1 s) denominator, so that the average of the second-by-second mean heart periods now equals the overall average heart period. The average of the second-by-second means thus provides an unbiased estimate of the overall average, and one obtains the same answer whether treating the subsets (s) as units or averaging the numerators over the common denominator. The net effect of this weighting is to increase the relative contribution of longer beats to the mean estimates, because they occupy a longer period of time. The weighted heart period mean for the first second of Table 2, for example, lies closer to the value of the longer beat rather than at the arithmetic center of the two beats that contribute to this interval. This is appropriate because real-time analysis entails analysis across time, not across beats. This time-weighting is computationally simple, and is equivalent to the time series approach used for illustration (Table 2). It permits valid real-time analyses of heart period data.

In summary, for analysis in cardiac time, heart period is already expressed in the units of analysis, and heart period data require no further weighting to meet the definitional requirement enumerated by Graham. For real-time analyses, however, the dimensions of heart period do not comport with the temporal units of analysis and must be weighted by time. The time-weighted heart periods have a common denominator expressed in the basic unit of analysis (s) and fulfill the definitional requirements for an unbiased estimate. Thus, heart period data can be analyzed either in cardiac time or in real time, but when analyzed in real time the heart period values should be time weighted. For analysis in cardiac time, heart period values are already scaled in the basic units of analysis (beats), and no further weighting is necessary.

Heart rate. An obverse time base problem arises in the analysis of heart rate data that relates to the applicability of heart rate measures (Graham, 1978b; Thorne, Engel, & Holmblad, 1976). When heart rate is analyzed in real time, the average of the second-by-second means yields an unbiased estimate of the overall mean for all seconds (see Table 1). This is due to the fact that heart rate (in beats/s or beats/min) is already expressed in the basic unit of analysis (time). In contrast, when heart rate data are analyzed in cardiac time, the average of the beat-by-beat heart rates does not equal the overall average heart rate (see Table 1). This is because the beat-by-beat heart rate estimates (in beats/s) are not scaled in the fundamental unit of analysis (cardiac units or beats). This creates a problem when analyzing heart rate data in units (e.g., beats) that do not correspond to the temporal dimension of the rate metric (beats/min).[4]

The natural units of analysis for rate data are temporal units, because time is the common denominator of rate (e.g., beats/min). Hence, the average of the means of rate over subsets of time would yield an unbiased estimate of the overall average rate. In contrast, beats can vary in duration, and rate data over these units is not appropriately scaled by time. This is reflected in the fact that the average 1.9 bps or 113.89 bpm (see Table 1) across beats does not equal the overall average heart rate, and thus does not provide an unbiased estimate of the overall rate. As noted by Graham (1978b), these beat-by-beat estimates of rate could be equalized into standard temporal units by multiplying the rates by the duration of the respective beat and dividing by the overall (2-s) interval (i.e., [1.11 * 0.9 + 3.33 * 0.3 + 1.25 * 0.8]/2 s = 1.5 bps), and the mean of the data would now quantitatively equal the definitional mean of 1.5 bps. The meaning of these weighted values is obscure, however, because the weighting would equate the estimates of each beat to a value of 0.5 and eliminate all variance (1.11 * 0.9/2 = 0.5 bps; 3.33 * 0.3/2 = 0.5; 1.25 * 0.8/2 = 0.5 bps). In short, beat-by-beat heart rates do not provide unbiased estimates of the overall heart rate, and they can not be meaningfully time weighted.

Summary and implications. These considerations reveal that the time base issue imposes constraints on the analysis of heart

[4] Graham (1978b) presented an illuminating 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, what is 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, the trips differ in length 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 yields 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 was only 60 miles, and the overall trip 120 miles.

rate and heart period data in cardiac and real time. In accord with Graham (1978b), the natural units for the analysis of heart period data are beats, whereas the natural units for heart rate data are seconds. Heart period data, however, can be appropriately analyzed in real time if the data are weighted by the duration of the beats. In contrast, heart rate data can only be properly analyzed in real-time units.

Conclusions

Some investigators have expressed a preference for heart period as a chronotropic metric (Jennings et al., 1974; Khachaturian et al., 1972), whereas others prefer heart rate, at least for infants (Graham & Jackson, 1970; Richards, 1980). Graham (1978a) provided a thorough review of the literature, including a further analysis of a wide array of data from both infants and adults, using both raw values and difference scores, and for data derived both within and between subjects. Graham concluded "while several criteria should be taken into account in deciding between period and rate, there is no reason to reject either measure out of hand on the basis of distributional properties" (Graham, 1978a, p. 491). She pointed out that neither metric has a consistent advantage for adult data, although for infants, rate may tend to be more normally distributed and evidence greater homogeneity of variance.

Although distributional properties do not provide for a definitive selection between the alternate chronotropic metrics, considerations related to biometrics and analytical flexibility reveal considerable advantages to heart period. Biometric evidence reveals that the transfer functions relating autonomic nerve traffic to chronotropic state are more nearly linear when chronotropic effects are expressed in the metric of heart period. The significance of the relative linearity between autonomic outflows, and heart period is that a given unit of heart period change represents a constant change in autonomic outflow independent of baseline. In contrast, the nonlinearities inherent in autonomic-heart rate relationships can introduce, ipso facto, apparent baseline dependencies and autonomic interactions into psychophysiological relationships. Psychophysiological relationships are comprised of two general sets of transforms, from antecedent conditions to central autonomic outflows, and from autonomic outflows to functional effects on visceral target organs. Nonlinearities in the latter set of transforms can complicate psychophysiological studies because they can distort or obscure lawful relationships in the transforms from antecedent conditions to central behavioral/autonomic states. Apparent baseline dependencies introduced by the nonlinearities inherent in heart rate, for example, can either exaggerate or attenuate manifestations of the LIV. Moreover, the use of heart rate as a metric can spuriously introduce apparent autonomic interactions in psychophysiological relationships. In short, biometric considerations suggest significant advantages to the use of heart period over heart rate as a chronotropic metric. It is important to note that this advantage is not dependent on an absolute linearity between autonomic outflows and heart period, but only on the fact that heart period is more linearly related to autonomic traffic than is heart rate.

Other factors, of course, must also be considered carefully in the selection of the optimal chronotropic metric. These include the distributional characteristics of the data relative to the assumptions of statistical tests, and the analytical flexibility of the metric relative to alternate time bases. The natural unit of analysis for heart period is cardiac time (beats), and for heart rate real time (seconds). A simple time weighting of heart period data permits appropriate analyses of heart period data in real time, whereas no parallel weighting permits analysis of heart rate data in cardiac time. In addition to biometric considerations, this confers considerable advantage to heart period as a chronotropic metric.

In the aggregate, the issues considered here suggest clear advantages, and minimal disadvantages, to the use of heart period as a chronotropic metric for adult subjects. For infants, distribution characteristics may confer some advantage to the use of heart rate over heart period. Many common statistical analyses are relatively robust to violations of normality and homogeneity of variance, however, and heart period would have considerable biometric and analytical advantages for infant studies as well. Ideally, data should be evaluated for conformity with assumptions of statistical tests regardless of the chronotropic metric employed. If assumptions are seriously violated, then alternate approaches should be followed. That may include the use of distribution-free statistical tests, or the heart rate metric. If heart rate is used, investigators may find it worthwhile to replicate their analyses in heart period to examine the potential impact of underling biometric relationships on the obtained pattern of results.

In summary, heart period would appear to offer considerable advantages over heart rate as a chronotropic metric. Although heart rate may be appropriate in some cases, investigators should be aware of the interpretive difficulties and analytical limitations inherent in heart rate metrics.

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