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METHODOLOGY

Autonomic interactions and chronotropic control of the heart: Heart period versus heart rate

KAREN S. QUIGLEY[a] AND GARY G. BERNTSON[b]

[a] Department of Psychology, Pennsylvania State University, University Park, USA
[b] Department of Psychology, The Ohio State University, Columbus, USA

Abstract

Autonomic control of the heart varies more linearly with heart period than with rate. Relative linearity confers a greater independence of basal autonomic activation and heart period changes. Thus, heart period appears to be more appropriate for characterizing cardiac phenomena such as autonomic interactions that involve significant baseline shifts. Simulated and published empirical data were used to demonstrate the importance of the chronotropic metric for characterizing autonomic interactions. Simulations revealed a significant autonomic interaction when heart rate, but not heart period, was the chronotropic metric. Published heart rate data also show a substantial autonomic interaction, whereas heart period data do not. These findings suggest that the choice of chronotropic metric can overstate the extent of autonomic interactions on cardiac chronotropic function.

Descriptors: Sympathetic, Parasympathetic, Cardiac chronotropism

Considerable confusion exists in the cardiovascular and psychophysiological literatures about whether heart rate or its reciprocal, heart period, provides the more appropriate representation of chronotropic control of the heart. Although the subject has been debated at some length (Berntson, Cacioppo, & Quigley, 1995; Graham, 1978; Rigel & Millard, 1992), most investigators have not offered an explicit rationale for choosing one measure or the other. Studies of autonomic control such as those characterizing autonomic interactions on cardiac chronotropism may lead to conflicting interpretations, depending on the chronotropic measure, because heart rate and period are not linearly related (Berntson, Quigley, Fabro, & Cacioppo, 1992; Parker, Celler, Potter, & McCloskey, 1984; Rigel & Millard, 1992; Stramba-Badiale et al., 1991). The simulated and published empirical data presented here illustrate the importance of the choice of chronotropic metric when characterizing autonomic interactions at the heart.

Recently, recommendations have been made for choosing the chronotropic measure of heart period instead of heart rate when characterizing cardiac phenomena that result from changes in autonomic control, especially when basal chronotropic function is greatly altered by the experimental manipulation (Berntson, Cacioppo, Quigley, & Fabro, 1994; Berntson et al., 1995; Parker et al., 1984). Recordings of spontaneous autonomic efferent nerve traffic and studies using autonomic nerve stimulation have revealed that heart period displays a more nearly linear relationship with underlying autonomic cardiac input than does heart rate (Berntson et al., 1992; Jewett, 1964; Parker et al., 1984). The greater linearity that characterizes the relationship between autonomic activation and heart period is especially striking for the parasympathetic division, although a strong linear component also is apparent in sympathetic effects on chronotropism. Although the relative linearity may arise from a combination of nonlinear processes (Dexter, Levy, & Rudy, 1989), the approximately linear relationship of cardiac efferent activity and heart period appears to be species general, as demonstrated in rats, rabbits, cats, dogs, and humans (Berntson et al., 1992; Carlsten, Folkow, & Hamberger, 1957; Ford & McWilliam, 1986; Jewett, 1964; Katona, Poitras, Barnett, & Terry, 1970; Parker et al., 1984; Rosenbleuth & Simeone, 1934). As such, a given increment in autonomic activation will lead to a relatively comparable increment in heart period for any baseline heart period level. The greater independence of changes in heart period from baseline level is most important for studies in which baseline chronotropic function varies substantially. Because significant baseline chronotropic shifts are inherent to stimulation studies estimating the extent of autonomic interactions on cardiac chronotropic control, heart period appears to be a more mechanistically and conceptually appropriate measure for describing these effects (Berntson et al., 1994, 1995; Parker et al., 1984).

Interactions between the sympathetic and parasympathetic innervations of the heart have been observed at both pre- and postjunctional sites in the heart (Levy, 1990). A prejunctional inhibitory influence of acetylcholine on sympathetic adrenergic terminals is well established, and a small facilitatory effect of

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Address reprint requests to: K. Quigley, Department of Psychology, Pennsylvania State University, 519 Moore Building, University Park, PA 16802, USA. E-mail: ksq1@psu.edu.

acetylcholine on norepinephrine release also has been postulated (Habermeier-Muth, Altes, Forsyth, & Muscholl, 1990; Loffelholz & Muscholl, 1969, 1970; Muscholl, 1980). Another prejunctional mechanism has been proposed to account for inhibition of acetylcholine by norepinephrine at parasympathetic terminals (Levy, 1990; McDonough, Wetzel, & Brown, 1986), although there is some question about whether this mechanism operates at any or all cardiac vagal terminals (Manabe et al., 1991). In addition, neuropeptide Y is known to be colocalized and released with norepinephrine at sympathetic terminals and has been implicated in a relatively longer term inhibitory effect on acetylcholine release from parasympathetic terminals (Gardner & Potter, 1988; Potter, 1987; Warner & Levy, 1989a, 1989b, 1990). Finally, a postsynaptic adenylate cyclase-dependent mechanism may also contribute to sympathetic-parasympathetic interactions (Isenberg & Belardinelli, 1984; Lerman, Wesley, DiMarco, Haines, & Belardinelli, 1988; Levy, 1990). These results suggest that cardiac autonomic interactions are complex.

The most prominent resultant interaction to affect cardiac chronotropic function is a parasympathetic inhibition of sympathetic effects on the heart, termed *accentuated antagonism* (Furukawa & Levy, 1984; Henning, Khalil, & Levy, 1990; Levy & Zieske, 1969; Stramba-Badiale et al., 1991; Urthaler, Neely, Hageman, & Smith, 1986). Accentuated antagonism reflects a progressively greater parasympathetically mediated slowing of heart rate with increasing levels of concurrent sympathetic activation (see Figure 3 in Stramba-Badiale et al., 1991; Urthaler et al., 1986). In the present study, we used simulations and experimentally derived data to examine the effect of the chronotropic metric on the quantification of autonomic interactions at the heart.

Methods

Simulations

Quantitative estimates of accentuated antagonism, with chronotropic state expressed in heart period (ms) and rate (beats per minute, or bpm), were derived from the model of Levy and Zieske (1969). This model of autonomic control of the heart was derived from direct cardiac efferent stimulations in the chloralose/urethane anesthetized dog and takes the form of a nonlinear regression equation empirically fitted to heart rate data. The composite regression equation used for the simulations was

$$\Delta HR = 19.64s - 17.95v - 1.225s^2 + 1.357v^2 - 1.523sv,$$

where ΔHR is the change in heart rate (in bpm), s is the frequency of sympathetic stimulation (in Hz), and v is the frequency of vagal stimulation (in Hz). Using Levy and Zieske's (1969) reported basal heart rate of 154 bpm, absolute heart rates and heart rate change scores for fixed levels of parasympathetic activation (0–8 Hz) were derived by using this equation for five levels of sympathetic activation frequency (0, 1, 2, 3, and 4 Hz). These values span the range of stimulation frequencies used by Levy and Zieske (1969). Absolute heart rate values were also converted to heart period and heart period change scores (in ms).

The contrast between heart rate and heart period was also illustrated by rate transformations on heart period data simulated without interactions. A linear equation describing the relationship between autonomic activities and chronotropic state of the heart in humans was derived by Berntson, Cacioppo, and Quigley (1993) based on published reports of direct stimulation and potent autonomic reflexes. The derived equation was

$$HP_{ij} = \beta - 230s_i + 1{,}713p_j + I_{ij},$$

where HP_{ij} is the chronotropic state of the heart expressed in milliseconds of heart period, β is the intrinsic or non-neurally mediated heart period, 230 and 1,713 are estimates of the sympathetic and parasympathetic dynamic ranges, respectively, in milliseconds of heart period in the human, s_i and p_j are the independent activities of the sympathetic and parasympathetic branches expressed as a proportion of the sympathetic and parasympathetic dynamic ranges, respectively, and I_{ij} represents sympathetic and parasympathetic interactions at the heart.[1] For the human, intrinsic heart period or β is known to vary considerably as a result of such factors as aerobic capacity, and thus β must be estimated on the basis of known features of the population of interest. The β used for the current simulation was 617 ms, which was derived from 10 studies in the literature reporting rate or period for normal supine males (see Table 1 in Berntson et al., 1993). This equation was used to derive functions for five basal levels of sympathetic activation (s_i = 0, 0.25, 0.5, 0.75, and 1.0) across the full dynamic range of activation of the parasympathetic division (p_j from 0 to 1 in 0.1-unit increments) with the interaction term (I_{ij}) set to zero. Absolute heart period data were then converted to heart rate and heart rate change scores (in bpm).

Empirical Data

The impact of the chronotropic measure on estimates of autonomic interactions can also be illustrated by the existing literature. Several studies of sympathetic-parasympathetic interactions on chronotropic control are summarized in Table 1, and the results are expressed in both heart rate and heart period. These studies were selected because they provided absolute heart rate values, heart period values, or both. The data shown in Table 1 represent the maximal interaction effect that was observed in the direction of accentuated antagonism. The deviation of the observed heart rate (in bpm) or heart period (in ms) with combined vagal and sympathetic stimulation (observed effect) from that predicted by a simple summation of the independent vagal and sympathetic effects (predicted effect) was expressed in an interaction index (observed effect − predicted effect/observed effect).

Results and Discussion

Figure 1 illustrates the simulated data obtained with the equation of Levy and Zieske (1969) that contains an interaction term for the autonomic control of the heart in heart rate (left) and heart period (right). The upper panels of Figure 1 illustrate absolute heart rate and period for each level of sympathetic activation, and the lower panels illustrate rate and period change scores.[2] The change score depictions (lower panels) highlight

[1] The simplified form of the interaction term, I_{ij}, may be parsed further into higher order polynomial components, that is, s_i^2, p_j^2, $s_i p_j$, and so forth, as the data dictate (e.g., Levy & Zieske, 1969).

[2] A different baseline heart rate or period was determined for each level of sympathetic activation at zero parasympathetic activation. Change scores were computed by subtracting the appropriate baseline for a given sympathetic activation level from each heart rate or period value over all levels of parasympathetic activation.

Table 1. *Effects of Single and Combined Stimulations of Sympathetic and Vagal Cardiac Efferents on Heart Rate and Heart Period*

Study[a]	Baseline	Vagal stimulation	Sympathetic stimulation	Combined predicted	Combined observed	Index[b]
Heart rate (bpm)						
Stramba-Badiale et al., 1991	120	70/−50	201/+81	151/+31	95/−25	2.24
Levy & Zieske, 1969						
Figure 1[c] ($N = 1$)	181	100/−70	260/+78	189/+8	120/−70	1.11
Figure 3 ($N = 10$)	154	97/−57	213/+59	156/+2	107/−47	1.04
Urthaler et al., 1986	147	116/−31	203/+56	172/+25	137/−10	3.50
Mace & Levy, 1983						
Adult dogs	130	53/−77	179/+49	102/−28	64/−66	1.42
Young dogs	139	90/−49	174/+35	125/−14	97/−42	0.67
Heart period (ms)						
Stramba-Badiale et al., 1991	520	960/+440	301/−219	741/+221	681/+161	−0.37
Levy & Zieske, 1969						
Figure 1[c] ($N = 1$)	331	600/+247	231/−99	479/+148	500/+184	0.20
Figure 3 ($N = 10$)	390	618/+228	282/−108	510/+120	561/+171	0.30
Urthaler et al., 1986	408	519/+111	321/−87	432/+24	476/+68	0.65
Mace & Levy, 1983						
Adult dogs	462	1,132/+670	335/−127	1,005/+543	938/+476	−0.14
Young dogs	432	667/+235	345/−87	580/+148	618/+186	0.20

[a]These studies were conducted in adult (Levy & Zieske, 1969; Mace & Levy, 1983; Stramba-Badiale et al., 1991) and young (Mace & Levy, 1983; Urthaler et al., 1986) dogs. Stramba-Badiale et al. (1991) used right vagal stimulation and exercise to activate the sympathetic efferents to the heart in awake dogs. The other studies used right stellate and right or left vagal stimulation in barbiturate or chloralose/urethane anesthetized subjects. [b]Interaction index values were computed by using the following equation: combined observed change score − combined predicted change score/combined observed change score. [c]Figure 1 contains an exemplar ($N = 1$) subject that is one of the 10 dogs shown in Figure 3. Different baseline values are reported for each stimulation condition; therefore, change scores do not necessarily summate to the mean basal value presented here (basal value/change score).

the interaction effect observed when sympathetic and parasympathetic activations increase concurrently. The lower left panel of Figure 1 illustrates an apparent substantial autonomic interaction in cardiac chronotropic control when heart rate is the measure. This interaction, in the direction of accentuated antagonism, is seen as a progressive enhancement of the effect of increments in parasympathetic activation with increments in sympathetic activation. In contrast to heart rate, the converted heart period data (lower right panel in Figure 1) are considerably more linear, with the exception of the highest frequencies of vagal stimulation. Moreover, the nearly parallel heart period functions indicate that the effects of combined sympathetic and parasympathetic activation do not deviate as much from a simple additive model, as was apparent for heart rate. These results suggest that an interaction such as that documented by Levy and Zieske (1969) is most apparent when heart rate is used as the chronotropic measure. Given the nonlinearity of heart rate with underlying autonomic input to the heart, the basal shift in heart rate that occurs with sympathetic or parasympathetic stimulation may notably alter the scaling between autonomic outflows and heart rate change. Indeed, when heart period is used as the chronotropic measure, the magnitude of the apparent interaction is substantially reduced. These data demonstrate that the magnitude of the resultant effect of autonomic interactions on cardiac control is different, depending on the choice of chronotropic measure.

Figure 2 illustrates the converse effect of a heart rate transform imposed on heart period data. Data in Figure 2 were derived from the equation of Berntson et al. (1993) for human data with the interaction term set to null. The upper panels illustrate absolute heart rate and period values, and the lower panels depict rate and period change. The lower right panel of Figure 2 illustrates the linearity inherent in the model equation. The lower left panel of Figure 2 illustrates these same data when converted to heart rate and demonstrates the apparent interaction effect that arises with a rate transformation. Moreover, this apparent interaction is in the same direction as the typically observed accentuated antagonism (cf. lower left panel of Figure 1). This statistical artifact derives from the hyperbolic shape of the transform function describing the relationship between autonomic outflows and heart rate and the progressive restriction of range that occurs as heart rate slows.[3]

These simulations demonstrate that the magnitude of the autonomic interaction depicted by heart rate data is substantially reduced when the data are converted to heart period (lower right panel of Figure 1). Conversely, when heart period data are simulated in the absence of an interaction term, an apparent interaction effect arises by simple conversion of heart period to rate (lower left panel of Figure 2). It thus appears that a considerable portion of the observed interaction between sympathetic and parasympathetic chronotropic control of the heart may arise from use of a metric that is nonlinear across its normal activation continuum.

[3]A progressive restriction of range occurs with slowing heart rate as is apparent from the upper left panel of Figure 1. Absolute heart rates (upper left panel) show that an increment in parasympathetic outflow at a lower activation frequency has a larger effect on heart rate than the same increment at a higher frequency of vagal activation.

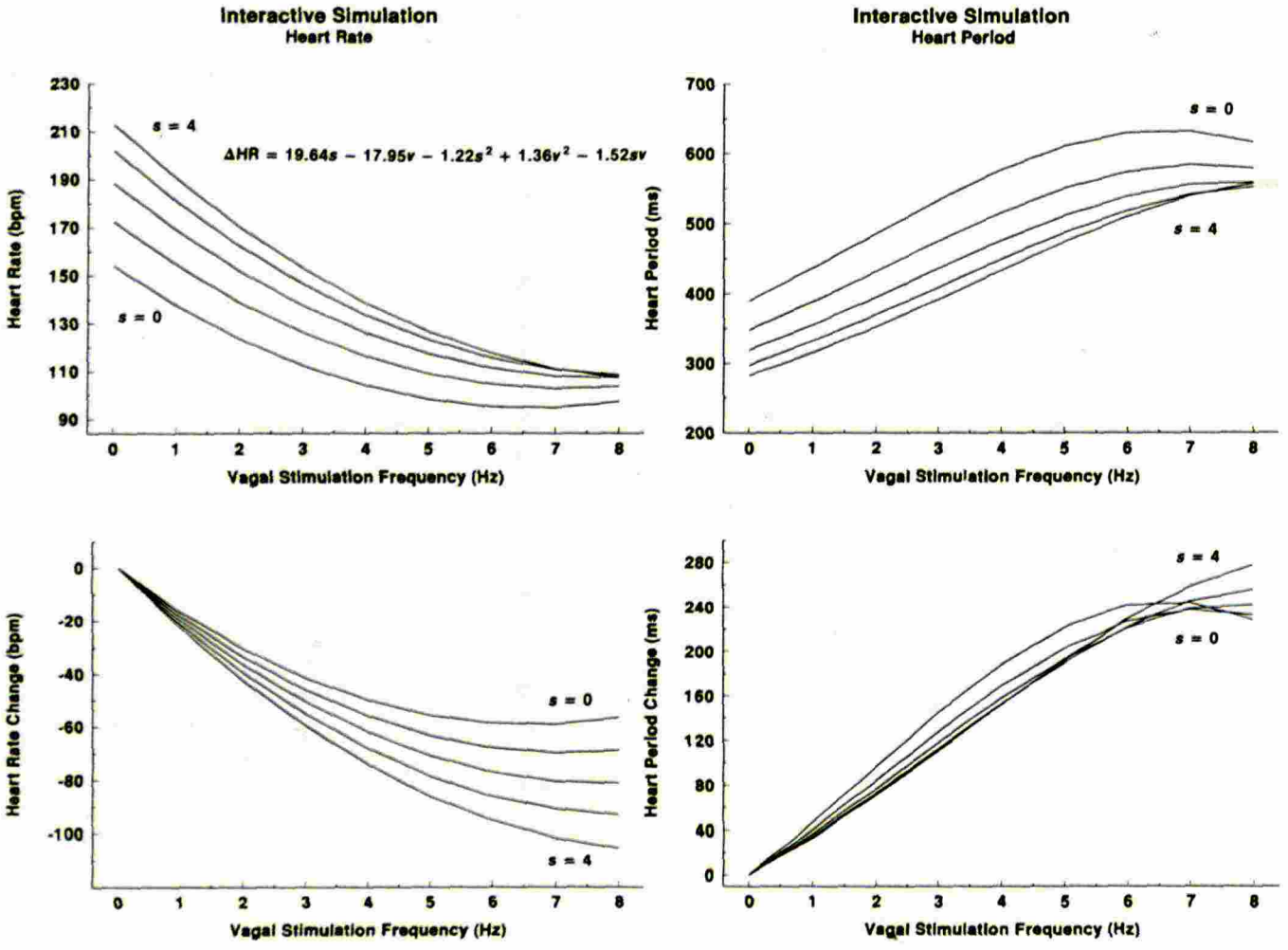

Figure 1. Interaction simulations using the model of Levy and Zieske (1969). Upper panels indicate absolute simulation data in beats per minute (bpm) or milliseconds (ms) as a function of vagal stimulation frequency. These panels show simulated data across the range of vagal stimulation used by Levy and Zieske (1969) for five levels of sympathetic activation. Lower panels depict change scores from basal heart rate or heart period. The data were modeled by using a regression equation containing a polynomial interaction term. The left panels illustrate the interaction that is described by the equation of Levy and Zieske (1969). The right panels demonstrate that only a minimal interaction remains when the simulated data on the left are converted to heart period.

As illustrated in Table 1, the literature also reveals that chronotropic interactions are generally observed when heart rate is the measure. This is evidenced by a deviation between the observed heart rate with combined parasympathetic and sympathetic stimulation and that predicted by a simple summation of the independent parasympathetic and sympathetic effects. For illustration, the extent of this deviation was expressed in an interaction index where index values approaching zero indicate no interaction, positive numbers indicate a vagal inhibition of sympathetic effects, and negative numbers a sympathetic inhibition of vagal effects. The interaction indexes derived from the published empirical studies in Table 1 ($M \pm SEM$: 1.66 ± 0.42) uniformly indicate a significant vagal inhibition of sympathetic effects on heart rate that is consistent with accentuated antagonism.

The interaction index was derived for heart period as described above, although the direction of autonomic effects on the sign of the interaction index is reversed. In comparison with heart rate, the heart period index values are not significantly different from zero and are directionally variable ($M \pm SEM$: 0.14 ± 0.15), indicating no consistent resultant interaction of sympathetic and parasympathetic innervations on heart period. These results do not appear to arise simply as a consequence of converting group mean heart rate to period values rather than converting individual values. Indeed, Stramba-Badiale et al. (1991) provided both mean heart period and rate based on individual data, and the example from Figure 1 of Levy and Zieske (1969; see Table 1) represents data for a single animal. The interaction index calculated for heart period for these two exemplars does not deviate substantially either from zero or from the estimates derived from the other studies. Thus, it appears that the interaction index values for the studies utilizing group mean data do not simply represent an artifact of converting group mean heart rate to heart period.

The data modeled in Figure 2 is especially relevant for psychophysiologists using human subjects and manipulations that produce wide variations in cardiac rate. The interaction effect

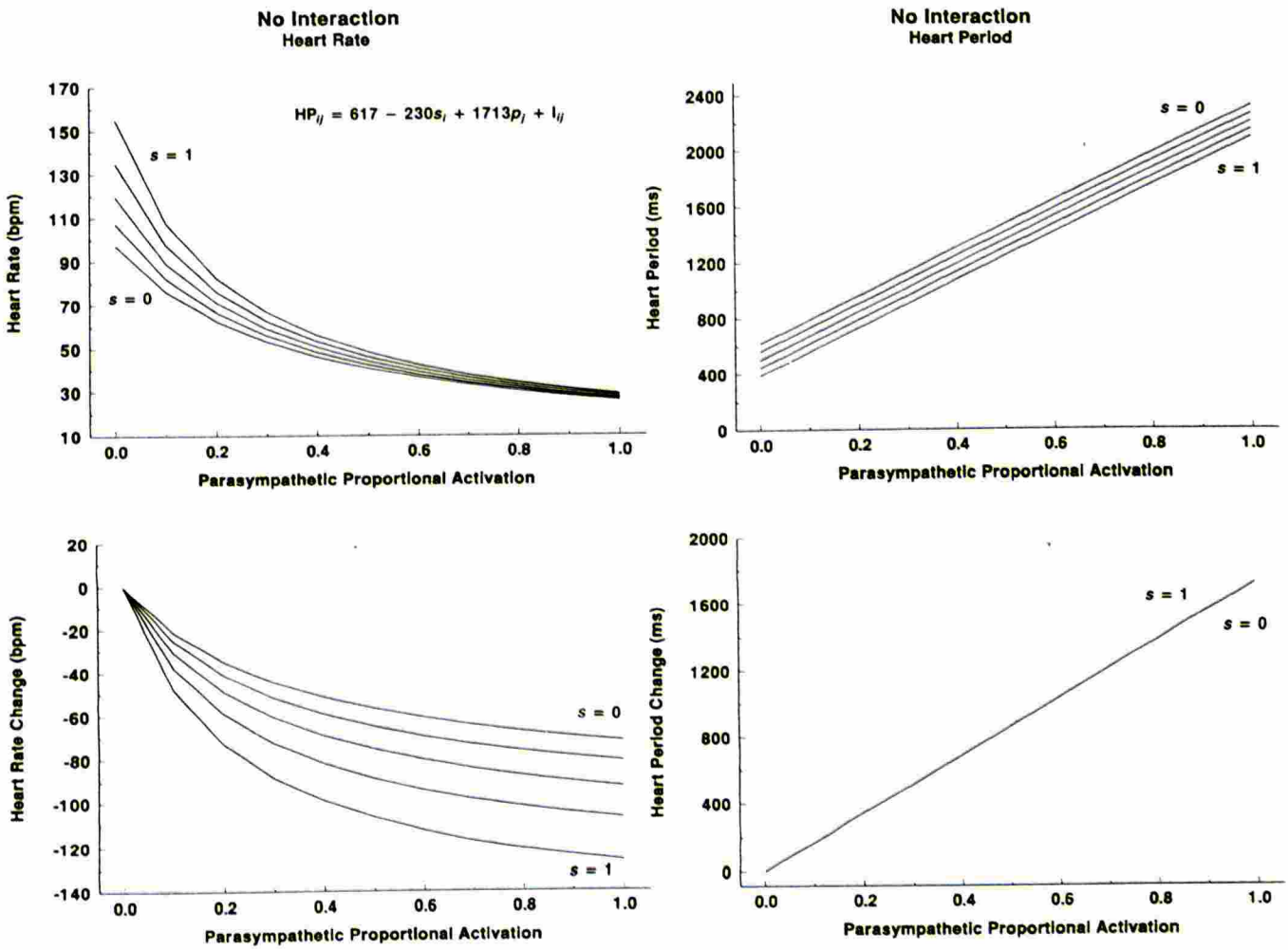

Figure 2. Noninteraction simulations using the autonomic space equation of Berntson, Cacioppo, and Quigley (1993) with the interaction term set to zero. Upper panels indicate absolute simulation data in beats per minute (bpm) or milliseconds (ms) as a function of proportional parasympathetic activation. These panels depict simulated data across the human dynamic range of vagal activation for five levels of sympathetic activation. Lower panels depict change scores from basal heart rate or heart period. The right panels demonstrate the linearity of simulated heart periods with respect to vagal activation frequency over the full range of sympathetic activation. The left panels demonstrate the apparent interaction effect that arises when the heart period data are converted to heart rate.

introduced by simple conversion of heart period to rate can be observed from the upper panels of Figure 2. Using published data summarized in Berntson et al. (1993: Table 4 and Figure 3) across postures, we can assume that resting basal s_i generally will fall between 0.25 and 0.75 (proportional activation units) on the sympathetic dynamic range, and p_j generally will fall between 0.1 and 0.5 (proportional activation units) on the parasympathetic dynamic range. These basal values can be seen in the upper panels of Figure 2 (where s_is of 0.25. 0.5, and 0.75 are depicted by the inner three of the five lines on the rate and period graphs, and p_j can be read from the abscissa). The interaction effect can be observed by holding either Δs_i or Δp_j constant and varying the other parameter. For example, for $\Delta p_j = 0.2$ (from proportional activation units 0.3 to 0.5), heart rate decreases by 13.5 bpm for $s_i = 0.25$ but decreases by 16.5 bpm for $s_i = 0.75$, for a discrepancy of 3 bpm. This effect is larger, however, for parasympathetic activational changes in the lower portion of the parasympathetic dynamic range. For example, by using $\Delta p_j = 0.2$ as in the previous example but considering the portion between 0.1 and 0.3 proportional units along the parasympathetic dynamic range, heart rate decreases by 26.2 bpm for $s_i = .25$ and by 34.8 bpm for $s_i = 0.75$ for a discrepancy of 8.6 bpm. These discrepancies may appear small compared with the magnitude of heart rate effects in some studies (e.g., the cardiac effects of a startle stimulus), but they can be a serious source of confound for smaller, less robust effects. Indeed, for the latter example, 8.6 bpm represents 33% of the heart rate change observed over $\Delta p_j = 0.2$ from 0.1 to 0.3 for $s_i = 0.25$. Most importantly, these examples only include autonomic changes within the normal basal range of chronotropic function and not the wider potential range over which potent autonomic reflexes or responses may alter chronotropic function. Thus, although the interaction effect arising from the use of heart rate is relatively modest for psychophysiological studies producing small-to-moderate effect sizes, the effects may be substantial for larger increases or decreases in autonomic activity. For a considera-

tion of more general consequences of the nonlinear heart period to heart rate transform for psychophysiology, the reader is referred to Berntson, Cacioppo, and Quigley (1995).

Mechanisms underlying chronotropic interactions have been demonstrated at both pre- and postsynaptic loci (Levy, 1990). With the exception of potential long-term effects of neuropeptide Y, however, the resultant chronotropic interaction may be smaller than previous results would suggest. Autonomic interactions may also be manifest in effects on cardiac contractility and, under some conditions, on conduction velocity (Furukawa & Levy, 1984; Henning et al., 1990; Levy, Ng, Martin, & Zieske, 1966; Levy & Zieske, 1969; Urthaler et al., 1986). Although the present analysis was limited to chronotropic control, potentially confounding contributions of shifts in basal autonomic state and potential alternative measures need to be considered when expressing interactions for any functional dimension of cardiac control. As a general strategy, interactions may be best expressed with a measure that is relatively impervious to the tonic state of the system. Heart period conveniently provides such a measure for studies of chronotropic control in which autonomic inputs to the heart are driving the cardiac phenomenon of interest and baseline shifts are inevitable. For other physiological systems, alternative strategies such as normalization techniques by which the effects of baseline activity are controlled statistically may be necessary to minimize the effects of the tonic state of the system on the characterization of interactions (Rigel & Millard, 1992).

The simulated and empirical data presented here suggest that much of the apparent autonomic interaction in chronotropic control may arise from the use of a nonlinear measure, namely heart rate. In contrast, because heart period is relatively linear with respect to underlying autonomic efferent outflows, the magnitude of phasic heart period changes are less sensitive to the basal heart period level. The relative independence of basal and phasic changes in chronotropic control constitutes an important advantage of using heart period when characterizing autonomic interactions. This is also true more generally for psychophysiological studies that entail autonomic stimulation or blockade and where large changes in basal cardiac chronotropic control are to be expected.

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