Sympathovagal balance: how should we measure it?

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Goldberger, Jeffrey J. Sympathovagal balance: how should we measure it? *Am. J. Physiol.* 276 (*Heart Circ. Physiol.* 45): H1273–H1280, 1999.—There are complex interactions between the sympathetic and parasympathetic nervous system inputs to the sinus node. The concept of "sympathovagal balance" reflects the autonomic state resulting from the sympathetic and parasympathetic influences. Despite widespread usage of a variety of heart rate (HR) variability parameters as indexes of sympathovagal balance, no index has been validated as a measure of sympathovagal balance. This study evaluated the utility of HR, HR variability, and a new parameter termed the vagal-sympathetic effect (VSE) as indexes of sympathovagal balance. The ideal parameter had to satisfy the following criteria: *1*) the index should vary similarly among subjects in response to different autonomic conditions; *2*) the variability in the index among subjects exposed to the same autonomic conditions should be small; and *3*) the response of the index to various autonomic conditions should reflect the underlying changes in physiological state and have a meaningful interpretation. Volunteers [8 men, 6 women; mean age 28.5 ± 4.8 (SD) yr] were evaluated for the effects of sympathetic and parasympathetic stimulation and blockade on HR and HR variability. VSE was defined as the ratio of the R-R interval to the intrinsic R-R interval. VSE and R-R interval consistently changed in the expected directions with parasympathetic and sympathetic stimulation and blockade. A general linearized model was used to evaluate the response of each parameter. VSE and R-R interval had r^2 values of 0.847 and 0.852, respectively. Natural logarithm of the low-frequency power had an r^2 value of 0.781 with lower r^2 values for all the other HR variability parameters. The coefficient of variation was also lowest for each condition tested for the VSE and the R-R interval. VSE and R-R interval best satisfy the criteria for the ideal index of sympathovagal balance. Because it is impractical under most conditions to measure the VSE as the index of sympathovagal balance, the most suitable index is the R-R interval.

autonomic; sympathetic; parasympathetic; heart rate

THE SINUS NODE is subject to both sympathetic and parasympathetic (vagal) effects that depend on the condition being evaluated. It is well accepted that conditions such as assuming an upright position, mental stress, and exercise are associated with an augmentation of sympathetic tone. In contrast, vagal tone is high during resting conditions. In normal subjects, both sympathetic and parasympathetic tone fluctuate throughout the day. The precise relationship between sympathetic and vagal tone and the nature of their interaction is not completely understood. Nevertheless, the concept of "sympathovagal balance" has arisen to characterize the autonomic state resulting from these sympathetic and vagal influences.

Heart rate variability analysis has emerged as a prevalent technique to assess autonomic influences on the heart. Support for its utility as an index of autonomic tone comes from data which demonstrate that heart rate variability is virtually abolished after sympathetic and parasympathetic blockade. Furthermore, under select conditions, certain frequencies of heart rate variability are accentuated in response to sympathetic and parasympathetic stimulation (25). Sympathovagal balance has emerged to describe the dual, opposing effects of the sympathetic and parasympathetic nervous systems on the sinus node. Whereas it is not well defined, this concept is meant to describe the net effects on the sinus node. Heart rate variability indexes such as the ratio of the low- (LF) to high-frequency (HF) power or the fractional LF power have been used to describe sympathovagal balance (22, 25). Nevertheless, lack of a precise definition or a uniform physiological construct for the sympathovagal balance has created much confusion. Excellent investigators in the field have diametrically opposing views regarding sympathovagal balance. Malliani et al. (21) noted that the reciprocal relationship between LF and HF seems to assess the sympathovagal balance. Chiou and Zipes (5) stated that their data suggest that LF/HF ratio can be used as an indicator of sympathovagal balance. In contrast, Eckberg (8) stated that "calculations of sympathovagal balance (ratio of LF to HF) may obscure rather than illuminate human physiology and pathophysiology."

Such opposing views indicate fundamentally different approaches to the issue. Sympathovagal balance is a concept that currently has no specific definition. The most precise way to actually characterize the sympathovagal balance is unknown. Montano et al. (24) assessed the changes in sympathovagal balance during graded orthostatic tilt using tilt angle as the index of sympathovagal balance. Bootsma et al. (4) also noted a relationship between the parameters of sympathovagal balance that they chose and tilt angle. Whereas logic dictates that with progressively increasing tilt angle, there is a progressive shift in the sympathovagal balance to increasing sympathetic effect, it is clear that tilt angle is a suboptimal measure of sympathovagal balance particularly because it cannot be generalized. Measurement of tilt angle is applicable only in situations where the subject is tilted and also does not account for interindividual differences in autonomic tone; it is unlikely that a subject with congestive heart failure tilted to 30° has the same sympathovagal balance as an age-matched control subject tilted to 30°. Montano et al. (24) and Bootsma et al. (4), based on their findings during graded tilt, have proposed that the measures

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they studied can provide a quantitative evaluation of sympathovagal balance. These measures include heart rate (4), normalized LF power (4, 24), and the ratio of LF to HF power (24). It is unknown which of these parameters is most suitable to describe the sympathovagal balance. However, it is clear that there may be situations in which even some of these measures of heart rate variability may not accurately reflect the sympathovagal balance, such as during exercise (2, 26).

To explore this issue further, it is necessary to have a broadly acceptable index of sympathovagal balance. To develop such a standard, one can define several criteria that it should fulfill. The index should vary similarly among subjects in response to different autonomic conditions. Furthermore, subjects exposed to the same autonomic conditions should have a minimal amount of variability in the index among them. Finally, the response of the index to various autonomic conditions should reflect the underlying changes in the physiological state and have a meaningful interpretation. Specifically, the index should provide information on the net effects of the sympathetic and parasympathetic nervous systems.

In this study, the above criteria were assessed for the R-R interval and for the standard time and frequency domain parameters of heart rate variability. In addition, a new index of sympathovagal balance is proposed that reliably captures its conceptual framework, namely the net effects of the sympathetic and parasympathetic nervous systems on the heart (sinus node). In the absence of any sympathetic or parasympathetic input to the sinus node, the sinus node fires at its intrinsic rate or R-R interval. When vagal effects predominate, the heart rate is less than the intrinsic heart rate; when sympathetic effects predominate, the heart rate is greater than the intrinsic heart rate. Thus the vagal-sympathetic effect (VSE) is defined as the ratio of the R-R interval to the intrinsic R-R interval (R-R_0)

$$\text{VSE} = \frac{\text{R-R}}{\text{R-R}_0}$$

where R-R_0 is defined as the R-R interval during autonomic blockade. The VSE is conveniently one when there is a perfectly balanced sympathetic-parasympathetic effect on the sinus node (i.e., at the intrinsic R-R interval). Furthermore, a VSE $>$ 1 reflects vagal predominance and a VSE $<$ 1 reflects sympathetic predominance. Thus the aim of this study was to assess the utility of the VSE, R-R interval, and heart rate variability measures as indexes of sympathovagal balance using a broad range of autonomic maneuvers.

METHODS

Subjects. Fourteen normal volunteers (8 men, 6 women; mean age ± SD: 28.5 ± 4.8 yr, range 22–38 yr) were studied at the Clinical Research Center at Northwestern Memorial Hospital. These subjects were a part of two studies evaluating the effects of sympathetic and parasympathetic stimulation and blockade on heart rate variability (1, 9), which were conducted on two separate days. Subjects were instructed to abstain from smoking or coffee consumption for 24 h before the study. No subjects had a history of diabetes mellitus, hypertension, syncope, palpitations, or cardiac disease. All subjects had a normal physical examination, normal resting electrocardiogram, normal hematocrit, and normal serum electrolytes. No subjects were taking medications. Written informed consent was obtained before the study. The study was approved by the Northwestern University Institutional Review Board.

Details of the study protocol have been previously described (1, 9). Briefly, an indwelling intravenous catheter was placed in the forearm through which normal saline solution was infused and through which drug infusions were performed. Subjects were attached to a cardiac monitor and an automated blood pressure device (Accutracker, Marquette Electronics). Electrocardiographic data were recorded on a commercially available computer system (Predictor I series 6.0, Arrhythmia Research Technology, Austin, TX) using an X, Y, and Z lead system. All recordings were made in 5-min segments, generally in triplicate, digitized at a sampling frequency of 1,000 Hz, and stored on optical disk for subsequent analysis.

On the first day of testing, baseline recordings were made on subjects in the supine position after a 15-min rest period. Recordings were then made while the subjects were in an upright tilt position at 70°, which results in reflex stimulation of the sympathetic nervous system. Premature termination of the tilt protocol occurred in four subjects because they experienced nausea and/or lightheadedness. However, at least one complete recording was obtained in all but one subject before the onset of those symptoms; data obtained after symptom onset were excluded from analysis. Subjects were then returned to the supine position, and their heart rate and blood pressure were allowed to return to baseline. Epinephrine infusion was begun at 2 μg/min and gradually increased to 50 $ng \cdot kg^{-1} \cdot min^{-1}$. Recordings were made after 10 min at this infusion rate. The infusion was then stopped, and each subject's heart rate and blood pressure were allowed to return to baseline values. Isoproterenol infusion was then started at 2 μg/min and gradually increased to 50 $ng \cdot kg^{-1} \cdot min^{-1}$. After 10 min at this dose, electrocardiographic recordings were made of each subject. One subject did not tolerate the maximum dose and recordings were made at a reduced dose of 25 $ng \cdot kg^{-1} \cdot min^{-1}$. The infusion was stopped, and we allowed time for the heart rate and blood pressure to return to baseline values. Subjects then performed a symptom-limited exercise on a bicycle ergometer with progressively increasing workloads. All subjects exercised to fatigue (mean exercise time 8.4 ± 2.4 min), achieving a mean maximal heart rate of 168 ± 12 beats/min (range 150–170 beats/min). Subjects were then returned to the supine position, and after a 2-min recovery period, three sequential 5-min electrocardiographic recordings were obtained. After a rest period to allow heart rate and blood pressure to return to baseline, we administered propranolol at a rate of 1 mg/min to a total dose of 0.2 mg/kg (12) to achieve β-blockade (with subjects in the supine position), and electrocardiographic recordings were obtained. Double autonomic blockade was achieved by administering atropine (0.04 mg/kg) intravenously over 2 min in the presence of the β-adrenergic blockade (12). Adequacy of double autonomic blockade was confirmed by near abolition of heart rate variability (1). Thus on the first day of testing, the conditions tested included various forms of sympathetic stimulation, β-adrenergic blockade, and double autonomic blockade.

On a second day, 10 subjects underwent further testing to evaluate the effects of parasympathetic stimulation and

blockade. Baseline recordings were made following a 15-min rest period. Recordings were then made during reflex parasympathetic stimulation with a phenylephrine infusion titrated to increase the systolic blood pressure by 20–30 mmHg. We have previously shown that there are no α-adrenergic effects of phenylephrine on heart rate variability (9). After phenylephrine was discontinued and the heart rate and blood pressure of the subjects returned to baseline values, we administered atropine (0.04 mg/kg) intravenously over 2 min to achieve parasympathetic blockade and recordings were made.

Heart rate variability analysis. The methodology has been previously described (1, 9). All 5-min recordings were visually examined and manually overread to verify beat classification. The mean R-R interval was calculated. The mean R-R interval was used for analysis rather than the heart rate because it is directly related to vagal nerve activity (15, 18). The standard deviation of the R-R intervals (SD), the root mean square of the successive R-R interval differences (MSSD), and the percentage of R-R intervals that differed by >50 ms (pNN50) were calculated for each 5-min recording. An autoregressive model was used to generate heart rate spectra for each 5-min recording. Power in the LF band from 0.04 to 0.15 Hz [in (beats/min)^2] was measured. Power in the HF band from 0.15 to 0.40 Hz [in (beats/min)^2] was also measured. The ratio of LF to HF power (LF/HF) was calculated from these values. The fractional low (%LF) and high-frequency (%HF) powers were calculated by dividing the individual values by the total power; the natural logarithms of the low (lnLF) and high (lnHF) frequency powers were also calculated.

Data analysis. For each subject, the results from the multiple recordings during each condition (except exercise) were averaged. After exercise, each of the three recordings was considered individually. Repeated-measures analysis of variance was used to evaluate the effect of the conditions tested on the VSE. Post hoc comparisons were performed with Scheffé's *F* test. Each parameter was analyzed using a general linearized model in which the response was the parameter and the factors were either *1*) the conditions and the subjects, or *2*) the conditions alone. This latter analysis attempts to explain the variability of the parameter only by the changes in condition, thereby excluding interindividual differences in the parameter. The ideal index of sympathovagal balance should not be dependent on subjects. The r^2 values obtained from the general linearized model were used to assess the proportion of the variability of an index due to the conditions and/or the subjects.

For each parameter, the coefficient of variation was calculated for each condition tested as the measure of interindividual variability in the parameter. The ideal index would have a low coefficient of variation for each condition tested.

Because it has been suggested that intense autonomic stimulation may saturate the heart rate variability changes (20), a second analysis was performed including only the conditions that resulted in R-R intervals between 1,000 and 600 ms (heart rate 60–100 beats/min). In addition, because the heart rate variability response to catecholamine infusion may be different from that observed with sympathetic neural stimulation (1, 16), an additional analysis was performed using only the data from the baseline recordings and during upright tilt. The increase in sympathetic tone during upright tilt is predominantly due to neural stimulation (1). All data are presented as means ± SD. A P value <0.05 was considered statistically significant.

RESULTS

Table 1 summarizes the data obtained for the R-R interval and the time and frequency domain heart rate variability indexes for each of the conditions tested. For the group, the intrinsic R-R interval (autonomic blockade) was 598 ± 42 ms (range 506–644 ms). On the first day at baseline, the mean VSE was 1.65 ± 0.26 confirming vagal predominance on the sinus node at rest; by analysis of variance, significant changes in the VSE were noted with the autonomic maneuvers tested ($P < 0.0001$). Sympathetic stimulation with upright tilt, epinephrine infusion, and isoproterenol infusion resulted in significant decreases in the VSE to 1.17 ± 0.10 ($P < 0.0001$), 1.27 ± 0.18 ($P < 0.0001$), and 0.82 ± 0.07 ($P < 0.0001$), respectively. After exercise, the VSE was significantly reduced on all three recordings (1.06 ± 0.15, 1.17 ± 0.16, and 1.23 ± 0.18; $P < 0.0001$ vs. baseline). After β-adrenergic blockade, the VSE was 1.54 ± 0.15 (P = not significant compared with baseline). On the second day, the baseline VSE was 1.75 ± 0.13. With parasympathetic stimulation (phenylephrine infusion), the VSE increased to 2.27 ± 0.16 ($P < 0.0001$). With parasympathetic blockade, the VSE decreased to 0.92 ± 0.07 ($P < 0.0001$). Figure 1 demonstrates the sequential changes in VSE, R-R interval, and heart rate variability after exercise. The VSE and R-R interval changed in the expected directions uniformly for all subjects after exercise, as well as with all

Table 1. *Results of heart rate variability analysis and VSE for conditions tested*

	Base 1	Tilt	Epinephrine	Isoproterenol	*Exercise 1*	*Exercise 2*	*Exercise 3*	β-Blockade	*Base 2*	PE	Atropine
R-R, ms	981 ± 139	693 ± 62	762 ± 119	489 ± 32	635 ± 82	698 ± 82	735 ± 92	921 ± 83	1034 ± 109	1335 ± 140	542 ± 58
SD, ms	70.8 ± 27.2	47.9 ± 17.9	45.1 ± 22.2	17.1 ± 5.2	29.4 ± 8.2	27.8 ± 9.2	36.7 ± 17.0	61.5 ± 25.2	71.7 ± 25.8	45.1 ± 19.1	8.0 ± 3.2
MSSD, ms	65.2 ± 43.4	21.2 ± 10.7	33.6 ± 24.9	5.6 ± 2.8	11.6 ± 8.2	15.3 ± 9.7	21.4 ± 12.9	53.2 ± 34.6	72.4 ± 42.4	53.6 ± 27.5	3.4 ± 3.8
pNN50, %	33.9 ± 23.1	4.5 ± 7.1	11.5 ± 15.9	0.1 ± 0.4	1.0 ± 2.0	2.7 ± 4.3	4.8 ± 5.5	25.0 ± 21.3	37.8 ± 24.1	32.8 ± 22.9	0.1 ± 0.2
LF, (beats/min)^2	3.24 ± 2.50	7.41 ± 4.92	3.77 ± 3.01	2.37 ± 1.57	1.95 ± 0.80	1.98 ± 2.20	2.82 ± 2.67	2.94 ± 1.44	2.70 ± 1.56	0.35 ± 0.37	0.07 ± 0.06
HF, (beats/min)^2	2.24 ± 1.85	1.64 ± 1.42	1.98 ± 2.05	0.76 ± 0.75	0.79 ± 0.66	0.56 ± 0.48	0.97 ± 0.84	2.16 ± 1.93	2.35 ± 1.87	0.32 ± 0.25	0.11 ± 0.24
LF/HF	1.98 ± 1.35	6.34 ± 3.30	2.56 ± 1.27	5.07 ± 3.05	3.59 ± 2.01	4.79 ± 3.42	5.31 ± 5.38	3.00 ± 2.67	1.92 ± 1.65	1.13 ± 0.44	3.78 ± 4.64
%LF	32.5 ± 10.3	38.1 ± 12.4	33.1 ± 9.0	23.6 ± 8.9	20.5 ± 10.0	29.5 ± 13.9	33.0 ± 13.8	34.1 ± 8.1	31.5 ± 9.1	24.3 ± 9.5	7.2 ± 4.7
%HF	21.9 ± 10.7	8.1 ± 4.6	16.4 ± 7.5	6.7 ± 4.6	9.0 ± 8.4	9.9 ± 8.7	13.3 ± 11.8	20.7 ± 12.9	25.9 ± 12.7	24.7 ± 10.2	9.1 ± 16.9
lnLF	0.93 ± 0.63	1.78 ± 0.62	1.07 ± 0.67	0.57 ± 0.76	0.60 ± 0.39	0.38 ± 0.73	0.72 ± 0.78	0.91 ± 0.53	0.72 ± 0.65	−1.67 ± 1.02	−3.30 ± 1.10
lnHF	0.45 ± 0.84	0.10 ± 0.92	0.29 ± 0.93	−0.85 ± 1.08	−0.52 ± 0.79	−0.94 ± 0.95	−0.55 ± 1.22	0.25 ± 1.16	0.37 ± 1.04	−1.65 ± 1.23	−3.68 ± 1.63
VSE	1.65 ± 0.26	1.17 ± 0.10	1.27 ± 0.18	0.82 ± 0.07	1.06 ± 0.15	1.17 ± 0.16	1.23 ± 0.18	1.54 ± 0.15	1.75 ± 0.13	2.27 ± 0.16	0.92 ± 0.07

Values are means ± SD; R-R, R-R interval; SD, standard deviation; MSSD, root mean squared successive difference; pNN_{50}, percent difference >50 ms; LF, low-frequency power; HF, high-frequency power; %LF, percentage LF; %HF, percentage HF, lnLF, natural logarithm of LF; lnHF, natural logarithm of HF; VSE, vagal-sympathetic effect; *base 1*, baseline recording on *day 1; base 2*, baseline recording on *day 2*; PE, phenylephrine.

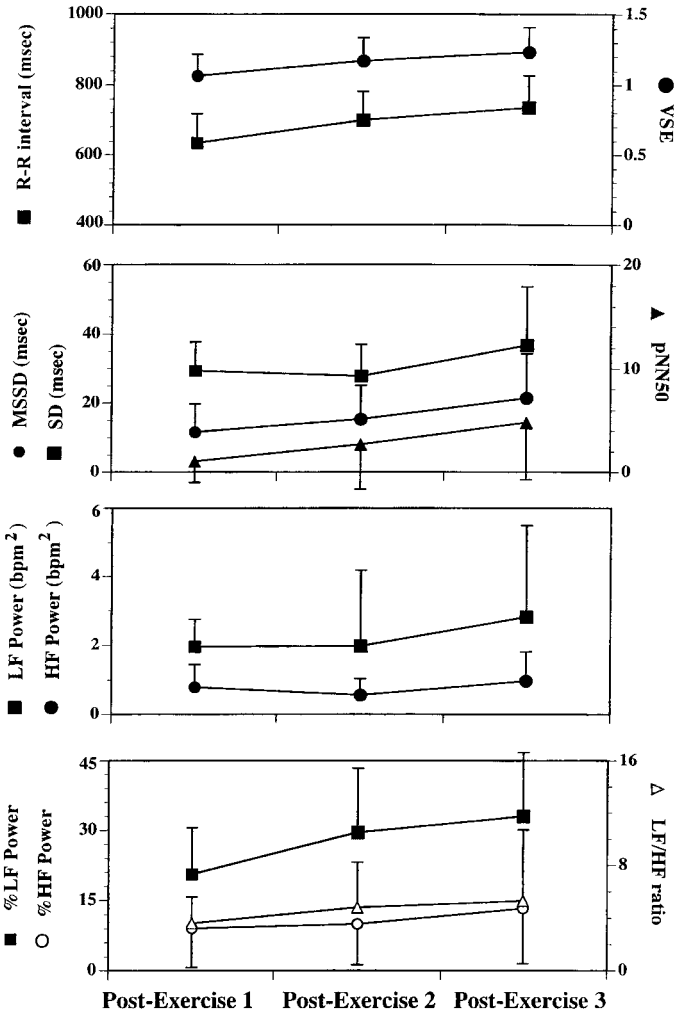

Fig. 1. Plots of R-R interval, vagal-sympathetic effect (VSE), standard deviation (SD), root mean squared successive difference (MSSD), percent difference >50 ms (pNN50), low-frequency (LF) power, high-frequency (HF) power, LF/HF ratio, %LF power, and %HF power for three sequential 5-min periods after exercise.

the other conditions tested. In contrast, none of the other conditions changed uniformly in the expected directions for all conditions tested (Fig. 1, Table 1).

The general linearized model was statistically significant for each parameter studied. The r^2 values from the generalized linear models are shown in Table 2. The VSE, R-R interval, and the lnLF had the highest r^2 values (0.934, 0.928, and 0.839, respectively) when both the condition and the subjects were included in the model. However, the ideal index of sympathovagal balance should not demonstrate a substantial amount of interpatient variability (for the same conditions). The reduction in r^2 values for the VSE, R-R interval, and the lnLF was fairly limited (0.847, 0.852, and 0.781, respectively) in the model that included only the conditions. In contrast, the r^2 values for the LF/HF ratio decreased from 0.496 to 0.195 when the subjects were not included in the model, suggesting that this parameter is predisposed to having significant interpatient variability. Thus the LF/HF ratio is not an ideal choice for an index of sympathovagal balance.

To assess the variability of the response of subjects to each condition, the coefficient of variation was measured for each condition for each parameter studied; the results are presented in Fig. 2. It is clear from Fig. 2 that the R-R interval and the VSE have the lowest coefficients of variation, which were always less than one-half the coefficients of variation of the other indexes at the same condition. Furthermore, the coefficients of variation values for the R-R interval and the VSE were never >16% for any condition.

When only the data with R-R intervals between 1,000 and 600 ms were considered, the general linearized model was statistically significant for each parameter studied. The r^2 values from the generalized linear model are shown in Table 3. The VSE, R-R interval, and the lnLF continued to have the highest r^2 values (0.846, 0.817, and 0.763, respectively) when both the condition and the subjects were included in the model, although they were reduced compared with those values obtained when all R-R intervals were included in the model. Furthermore, in this heart rate range, there was a more pronounced drop in r^2 values when only the conditions were included in the model. The coefficients of variation demonstrated similar findings to those shown in Fig. 2. For the R-R interval and the VSE, the coefficients of variation varied between 0.1 and 14.4% for all the conditions studied. For the other parameters, the coefficients of variation varied between 18.5 and 947% for all the conditions studied.

Examining the data from only the baseline recordings and during upright tilt, we found that the general linearized model was still statistically significant for each parameter studied. The r^2 values from the generalized linear model are shown in Table 4. The VSE and R-R interval continued to have the highest r^2 values (0.917 and 0.921, respectively) when both the condition and the subjects were included in the model, with a substantial drop in r^2 values when only the conditions were included in the model (0.690 and 0.725, respectively). The heart rate variability parameters generally demonstrated higher r^2 values when only the baseline and tilt conditions were included in the analysis but

Table 2. *r^2 values for generalized linear models using either condition alone or both condition and subject as factors explaining variability in the indicated parameters*

	Model	
	Condition and subject	Condition
R-R	0.928	0.852
VSE	0.934	0.847
SD	0.670	0.547
MSSD	0.637	0.494
pNN50	0.624	0.490
LF	0.564	0.393
HF	0.514	0.255
LF/HF	0.496	0.195
%LF	0.544	0.401
%HF	0.544	0.289
lnLF	0.839	0.781
lnHF	0.722	0.521

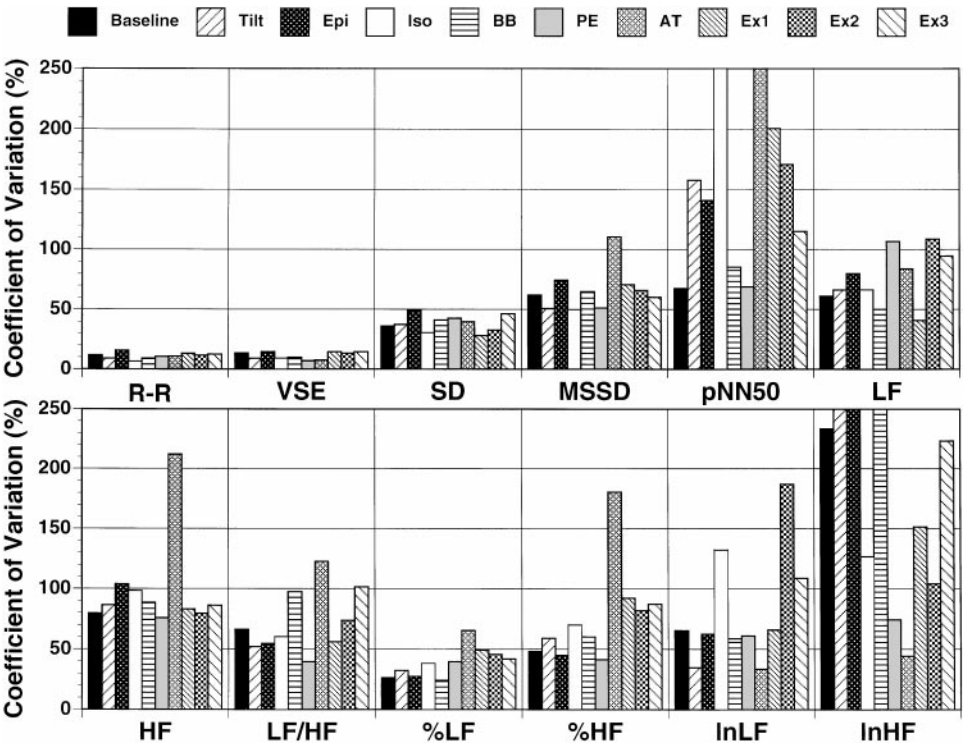

Fig. 2. Plot of coefficients of variation for each condition studied and for each indicated parameter. Values of coefficient of variation that were >250% were cut off for graphical display at 250%. R-R, R-R interval; Epi, epinephrine infusion; Iso, isoproterenol infusion; BB, β-blockade; PE, phenylephrine infusion; AT, after atropine; Ex1, 2, 3, sequential recordings made after exercise.

with a substantial drop in r^2 values when only the conditions were included in the model. The coefficients of variation demonstrated similar findings to those shown in Fig. 2. For the R-R interval and the VSE, the coefficients of variation varied between 8.9 and 13.6%. For the other parameters, the coefficients of variation varied between 27.3 and 947% for all the conditions studied.

DISCUSSION

Given the controversy in the literature regarding the concept of sympathovagal balance, this study was designed to test which parameters might provide the best indicator of sympathovagal balance. To accomplish this, the following criteria were established: *1*) the index should vary similarly among subjects in response to different autonomic conditions; *2*) the variability in the index among subjects exposed to the same autonomic conditions should be small; and *3*) the response of the index to various autonomic conditions should reflect the underlying changes in the physiological state and have a meaningful interpretation. For each parameter (VSE, R-R interval, and the time and frequency domain measurements of heart rate variability) evaluated, the model was significant, indicating that it can be used as an index of sympathovagal balance. However, the R-R interval and the VSE best fulfill the

Table 3. *r^2 values for generalized linear models using either condition alone or both condition and subject as factors explaining variability in the indicated parameters with the extremes of heart rate excluded*

	Model	
	Condition and subject	Condition
R-R	0.817	0.647
VSE	0.846	0.582
SD	0.574	0.339
MSSD	0.577	0.331
pNN50	0.611	0.384
LF	0.584	0.306
HF	0.545	0.155
LF/HF	0.610	0.194
%LF	0.450	0.191
%HF	0.625	0.202
lnLF	0.763	0.547
lnHF	0.728	0.224

Only heart rates of 60–100 beats/min were included.

Table 4. *r^2 values for generalized linear models using either condition alone or both condition and subject as factors explaining variability in the indicated parameters with only the baseline recordings and those made during upright tilt*

	Model	
	Condition and subject	Condition
R-R	0.921	0.725
VSE	0.919	0.690
SD	0.725	0.197
MSSD	0.751	0.358
pNN50	0.773	0.427
LF	0.653	0.291
HF	0.667	0.027
LF/HF	0.847	0.436
%LF	0.796	0.010
%HF	0.863	0.010
lnLF	0.770	0.539
lnHF	0.776	0.021

above criteria. The variability noted in the R-R interval and the VSE is mostly explained by the changes in the conditions as documented by the high r^2 values. Within each condition, they demonstrated the lowest intersubject variability (lowest coefficient of variation). Finally, when the sympathovagal balance was altered toward increasing sympathetic effect, the R-R interval and the VSE uniformly decreased, and when the sympathovagal balance was altered toward increasing parasympathetic effect, the R-R interval and the VSE uniformly increased. None of the heart rate variability parameters performed as well as either the R-R interval or the VSE. However, of these parameters, the natural logarithm of the LF power was the best predictor of the sympathovagal balance. Because it is impractical under most conditions to measure the VSE as the index of sympathovagal balance, the most suitable choice is the R-R interval.

The term sympathovagal balance has been used extensively in the literature and has frequently been characterized by the LF/HF ratio or the %LF power. However, the gold standard for measuring the sympathovagal balance is unknown. It is therefore difficult to assess the utility of the LF/HF ratio or the %LF power as indexes of sympathovagal balance. To evaluate sympathovagal balance, a concept similar to the VSE was proposed by Rosenblueth and Simeone (31). They defined the effects of the sympathetic and parasympathetic nervous systems on the heart rate in cats; the influences on the heart rate were found to be defined by the following formula

$$HR = m \times n \times HR_0$$

where HR is the heart rate, HR_0 is the intrinsic heart rate, m is the sympathetic influence ($m > 1$), and n is the parasympathetic influence ($n < 1$). Katona et al. (14) extended this relationship to humans. The VSE is related to the product $m \times n$ by the formula

$$VSE = \frac{1}{m \times n}$$

The VSE is a robust index of the net effects of the sympathetic and parasympathetic nervous systems on the sinus node. Whereas it is not the only potential index of sympathovagal balance, it certainly provides a physiologically appropriate descriptor of the sympathovagal balance. Moreover, it can be applied in all autonomic conditions tested; it does not have the limitation of the heart rate variability measures in certain conditions, such as exercise (2, 26). From a theoretic perspective, the VSE should be a better measure of sympathovagal balance than the R-R interval; clearly, a heart rate of 90 beats/min will reflect different sympathovagal balances in individuals with intrinsic heart rates of 90 and 120 beats/min. However, by the criteria set out in this study, there does not appear to be much of an advantage to using the VSE as the index of sympathovagal balance over the R-R interval. Calculation of the VSE is based on the intrinsic R-R interval, which is determined after double autonomic blockade. It is possible that the excess tachycardia associated with pharmacological parasympathetic blockade (28) interferes with the utility of this measurement. Furthermore, routine clinical use of the VSE is impractical because it requires determination of the intrinsic R-R interval by pharmacological blockade of the sympathetic and parasympathetic effects on the sinus node.

The R-R interval therefore seems to be the best available option to serve as an index of sympathovagal balance. Although Bootsma et al. (4) tacitly assumed this was the case in their analysis of sympathovagal balance, it is clear that this is not yet widely accepted. In the studies by Montano et al. (24) and Bootsma et al. (4), the R-R interval or heart rate was a strong predictor of sympathovagal balance as measured by tilt angle. Whereas some of the heart rate variability parameters were also strongly correlated with tilt angle, it is difficult to infer which of these parameters is superior because the utility of tilt angle as a measure of sympathovagal balance is unknown.

Whereas the R-R interval and VSE may serve as indexes of the net effects of the sympathetic and parasympathetic inputs to the sinus node, they do not provide a global assessment of sympathetic or parasympathetic tone. Assessment of sympathovagal balance using the R-R interval as its surrogate does not presume any a priori knowledge of the levels of sympathetic or parasympathetic tone or their relationship to each other. It is clear, for example, that an individual may attain a heart rate of 90 beats/min by autonomic withdrawal (i.e., double blockade) or by sympathetic stimulation (i.e., upright tilt or exercise); furthermore, there may be many combinations of sympathetic and parasympathetic tone that may result in the same heart rate. In other words, the sympathovagal balance characterized by the R-R interval is not unique in that one value may clearly reflect different autonomic states. It is possible that the heart rate variability measures can contribute to the global assessment of sympathetic or parasympathetic tone by providing an index of the magnitude of the contributions of the sympathetic and parasympathetic nervous systems at any particular level of sympathovagal balance.

To clarify the relative roles of sympathovagal balance, VSE, heart rate, and heart rate variability it is useful to consider the following construct. Both the sympathetic and parasympathetic inputs to the sinus node can be characterized by a tonic level of activity and by the modulation of this activity (for example by respiration in the case of the parasympathetic input). The VSE and R-R interval, as indexes of sympathovagal balance, provide an index of the net effects of the autonomic input to the sinus node without regard to the individual levels of parasympathetic and sympathetic tone or their modulation. Thus a change in these parameters cannot be interpreted as either an increase in sympathetic tone or a decrease in parasympathetic tone (or vice versa); the change may reflect either one or a combination. Because it is not possible to presume any specific relationship (i.e., reciprocal) between sympathetic and parasympathetic tone (18, 27), it is best to

consider the R-R interval (as a surrogate of the sympathovagal balance) only as the net result of all the autonomic influences on the sinus node. Not surprisingly, the physiological correlates of heart rate variability are somewhat more complex. It is clear that in certain situations, heart rate variability provides an index of the sympathovagal balance, but this is not universally applicable. Heart rate variability most reliably provides a measure of the modulation of the sympathetic and parasympathetic inputs to the sinus node. This information is not available from the VSE or R-R interval and likely represents an important component of the analysis of autonomic influences on the heart.

Limitations. The present study presupposes that the concept of sympathovagal balance exists, is useful to characterize, and can be quantified. However, the lack of a gold standard for sympathovagal balance makes the identification of a suitable index difficult. Nevertheless, to date, many investigators have proposed using a variety of parameters based on testing under limited conditions. Whereas these parameters may provide a suitable index under certain conditions, their general use cannot be justified. This study focused on defining an index of sympathovagal balance based on the desired characteristics of this index and the applicability to a wide variety of conditions.

Whereas the present study tested a wide variety of conditions, they are not comprehensive. In addition, some conditions may have complex autonomic effects. For example, exercise is a complex condition in which the intensity of exercise and the timing of evaluation (during exercise versus recovery) may affect the observed autonomic changes and heart rate variability measurements (1, 2, 23, 26, 29, 30). Changes in the autonomic state may also have secondary effects on other factors such as respiration, which also may affect these measurements.

This study was conducted in normal individuals. It is possible that the R-R interval and VSE would be inadequate indexes of sympathovagal balance in diseased populations due to the potential presence of (potentially subclinical) sinus node dysfunction and the use of medications that alter sinus node function.

Implications. The importance of autonomic tone in cardiac disease has become widely appreciated. Because the presence of heart rate variability is clearly due to autonomic effects on the sinus node and because its measurement is fairly easy to perform noninvasively, the use of heart rate variability as an index of sympathovagal balance has skyrocketed. This study demonstrates that the simpler measure of the mean R-R interval is a better index of the sympathovagal balance. In contrast, heart rate variability indexes provide a better measure of the modulation of autonomic input to the sinus node.

The prognostic importance of heart rate variability following myocardial infarction has been clearly demonstrated (3, 17, 32, 36). These findings have even been generalized to a community-based population (33, 34). Similarly, the prognostic importance of heart rate following myocardial infarction has been clearly demonstrated (10, 19), and these findings have also been generalized to community-based populations (7, 13). The relative prognostic importance of heart rate and heart rate variability has been debated (6, 17). Importantly, a covariance of heart rate and heart rate variability has been recognized (17, 34). Several investigators (17, 33) have noted that heart rate variability parameters are predictors of prognosis even when heart rate is included into multivariate models. It is therefore likely that the modulation of the sympathetic and parasympathetic inputs to the sinus node has independent importance in addition to the sympathovagal balance. Interestingly, specific measures of autonomic responsiveness using provocative maneuvers (i.e., response to a bolus of phenylephrine) have also been shown to be important prognostic markers (11, 35). It is possible that cardiac autonomic evaluation needs to occur in a continuum with the R-R interval serving as a global measure of sympathovagal balance, heart rate variability as a measure of autonomic modulation by respiratory and vasomotor activity, and baroreflex sensitivity as a measure of autonomic responsiveness. Further understanding of these tests of autonomic function are necessary to relate their prognostic roles to the underlying pathophysiological derangements.

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