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Heart Rate Variability as a Prognostic Tool in Cardiology

A Contribution to the Problem From a Theoretical Point of View

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Background Recent clinical studies have proposed standard deviation of heart rate as a diagnostic tool for the outcome of cardiac infarction. Mathematical analysis of heart rate variability shows that heart rate is influenced by different frequency components derived from different parts of the autonomous nervous system. In the experimental part of this study, we investigated the possibility of calculating a variable describing the parasympathetic branch of the autonomous nervous system exclusively.

Methods and Results In 60 healthy volunteers, heart rate was measured to 1 millisecond during two different conditions: 5 minutes of rest, and 5 minutes of intermittent handgrip dynamometry; the latter is known to increase sympathetic arousal selectively. Heart rate was found to be lower at rest (65.9 ± 9.7 beats per minute) than during dynamometry (72.8 ± 10.4 beats per minute, $P < .001$). Respiratory sinus arrhythmia (RSA) calculated from the mean absolute differ-

ences between successive heart beats showed no significant change (3.01 ± 1.62 beats per minute at rest versus 2.97 ± 1.30 beats per minute during dynamometry). In contrast, standard deviation increased from 5.19 ± 1.98 to 9.22 ± 3.56 beats per minute ($P < .001$).

Conclusions It can be concluded from these data as well as from other plots presented in this article that RSA is a measure of the parasympathetic vagal tone, whereas standard deviation is increased by both sympathetic and parasympathetic arousal. Clinical evidence and data from physiological experiments are presented to show that a selective measure of vagal tone like RSA may offer advantages over standard deviation as a prognostic tool in cardiology. (*Circulation*. 1994;90:1078-1082.)

Key Words • myocardial infarction • heart rate • nervous system, autonomous • prognosis • Special Reports

The prognostic value of heart rate variability (HRV) with respect to survival from and outcome of myocardial infarction has attracted increasing interest. With the Holter ECG, a large amount of patient data can be collected easily and noninvasively. In addition to the shape of the ECG, irregularities in the cardiac rhythm have received attention. Because HRV mirrors autonomic equilibrium, it is not surprising that recent studies revealed prognostic possibilities for HRV measurements following myocardial infarction. Although the influence of the autonomous nervous system (ANS) on HRV was recognized early in this century,¹ only recently have several studies²⁻⁵ made it clear that parasympathetic and sympathetic nervous activities influence HRV at different parts of the frequency spectrum.

At first glance, standard deviation (SD), widely accepted as a statistical measure of dispersion, would appear to be the most obvious measure of HRV, and it has gained popularity for this purpose. For example, Casolo et al⁶ proposed a relation between prognosis subsequent to myocardial infarction and SD based on

24-hour recordings of RR intervals. The SD of heart rate appears to be significantly decreased during the early phase of myocardial infarction, and this observation was related to clinical and hemodynamic indexes of severity. Although the prognostic value seems convincing in this study,⁶ the pathophysiological basis remains unclear, and therefore the method's reliability is questionable.

There are several effects that contribute to total HRV and therefore to SD. Besides patient activity, a multitude of endogenous physiological rhythms influence heart rate during a 24-hour period. Beginning with the fastest, the following main periods may be distinguished:

(1) Respiratory sinus arrhythmia (RSA) is mediated by respiration and is strongly controlled by parasympathetic activity. The short response time typical of the parasympathetic system is responsible for this relation. This is supported by a wide range of studies on the dose response to atropine.^{2,4,7} Depending on respiratory rate, RSA is usually observed in the narrow band of heart rate variations ranging from 2 to 5 seconds. Sympathetic nervous system activity appears to be too slow to influence this frequency band.⁵ In a clinical study,⁸ RSA and therefore parasympathetic activity were found to be significantly reduced in patients 2 weeks after myocardial infarction.

(2) "Medium" waves of HRV (period length, 7 to 15 seconds): Parasympathetic as well as sympathetic influences are apparent in this frequency band, which in-

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cludes the adrenergically mediated 10-second rhythm of blood pressure regulation. Slow respiration contributes RSA components in this band.

(3) "Slow" waves of HRV (period length, >20 seconds) are considered to be sympathetic in origin. Their amplitude is primarily inhibited by sympathetic blockers.⁹ Augmentation of the sympathetically mediated low-frequency variations of heart rate was found in cardiomyopathy.¹⁰ Slow waves are also augmented by handgrip dynamometry, which is known to selectively increase sympathetic arousal.¹¹ In hypertensive patients, the contribution of slow waves compared with RSA was found to be significantly higher, indicating a shift toward sympathetic dominance.¹²

(4) HRV variations with a period in the minute range are the consequences of neurohumoral oscillations in the epinephrine-norepinephrine and/or angiotensin levels in the circulating blood. Little attention has been devoted to these oscillations in cardiac disease.

(5) Hour rhythms (3-, 4-, or 6-hour period lengths) can be considered submultiples of the circadian rhythm and are found in body temperature. They can be drastically increased by stresses such as night and/or shift work.¹³ Here, the circadian system reacts by multiplying its frequency, like a flute that vibrates with its overtone if blown too forcefully.

(6) During rapid eye movement (REM) stages of sleep, additional HRV patterns can emerge that reflect sympathetic and parasympathetic arousal.¹⁴ These patterns normally follow the 1.5-hour rhythms of REM sleep periodicity.

(7) Circadian rhythms appear in almost every Holter ECG and reflect alterations in ANS equilibrium throughout the day. Studies on shift workers have shown that the circadian amplitude of heart rate is significantly reduced by this stress. Heckmann and Busch¹⁵ emphasized that the circadian variation is significantly reduced immediately after myocardial infarction but regenerates over a period of weeks. The circadian variation may also be influenced by antihypertensive agents as described in rats.¹⁶

Because so many effects, originating from different neurohumoral systems, may contribute to HRV, the diagnostic and prognostic values of total variability measured by a parameter like SD may be questionable. A parameter describing just one branch of the ANS may be more reliable. Frequency analysis of HRV offers differentiation of the rhythms described above. If only parasympathetic arousal is of interest, RSA would appear to offer the best parameter.

This study reports a comparison between heart rate SD, a quantity used in cardiological prognosis, and RSA, a quantity known to reflect cardiac vagal activity. Both quantities can be calculated easily from RR interval data obtained with a Holter ECG.

Methods

The experiments were performed on 60 healthy supine volunteers in three parts.

In part 1, after volunteers rested for 20 minutes while supine in a quiet room under constant conditions, heart rate during 5 minutes of rest was recorded and used for further calculations.

In part 2, the period with quiet respiration (part 1) was followed by 15 seconds of breath holding during deep inspiration, another 30 seconds of quiet respiration, and 15 seconds of

expiratory breath holding. Respiratory maneuvers are known to alter the activity of the parasympathetic branch of the ANS. This part of the experiments is used only for Fig 1.

In part 3, 5 minutes of intermittent hand dynamometry followed. The dynamometry consisted of 5 seconds of maximal and 1 minute each of 70% and 40% maximal voluntary handgrip contraction strength interspaced by periods of rest. Handgrip dynamometry is known to activate the sympathetic branch of the ANS.¹¹

Chest wall ECGs were recorded and stored in digital form during the experiment. RR intervals were determined offline to 1 millisecond. A computer program that uses matched filtering of the ECG data was developed to recognize the R peaks. As a check, all QRS complexes were plotted, synchronized for the R peak. False R peaks could readily be recognized visually. Experiments with >1% false R peaks were excluded from further processing.

Premature beats and the first following heartbeat were excluded by deleting all values >20% below or above the previous intervals. The interbeat intervals were converted to heart rate. Mean and SD values of heart rate were calculated separately for each part of the experiment. RSA was calculated using the mean absolute difference between each heartbeat interval and the successive one.¹⁷ This procedure is even simpler than the calculation of SD. RSA was calculated separately for the two parts of the experiment.

To display data from each individual experiment (Fig 1), successive 1-minute periods of heart rate data were used for the computation of SD and RSA. After each calculation, the frame was moved by 10 seconds, and another minute of heart rate data was investigated. This process gives a moving frame time series of RSA and SD.

SD of all experiments was plotted against RSA, and the respective regression lines were computed separately for the two experimental conditions. The two regression lines were tested for parallelism using a technique described by Kleinbaum and Kupper.¹⁸ All other regression coefficients were tested for statistical significance by a one-sided *t* test.

Results

The Table shows the mean values of heart rate, SD, and RSA during rest and during dynamometry for all subjects. It can be seen that heart rate increases together with SD, whereas RSA does not alter significantly during dynamometry.

A plot of SD of heart rate versus RSA was made for each experiment. Fig 1 shows one experiment in which the effects of parasympathetic and sympathetic activity can clearly be seen. During rest (+), parasympathetic activity is at a medium level. During inspiration (I), a lower level of parasympathetic activity was achieved, whereas during expiration (E), parasympathetic activation increased. During rest as well as during respiratory maneuvers, expiration, and inspiration, SD displays a more or less linear relation with RSA. Increasing parasympathetic activity also increases RSA and SD simultaneously.

During the dynamometric part of the experiment, the data display a different slope. Handgrip dynamometry at 40% strength (4 in Fig 1) increases SD much more than RSA. This effect is even more pronounced at 70% strength (7 in Fig 1), where RSA does not increase at all.

In Fig 2, a similar diagram is shown for all 60 subjects. Here, RSA and SD were calculated for the entire 5 minutes of rest and for the following 5 minutes of dynamometry separately. A positive nonlinear correlation can be recognized during rest ($R=.78$, $P<.001$). During dynamometry, SD exhibits a distinct increase

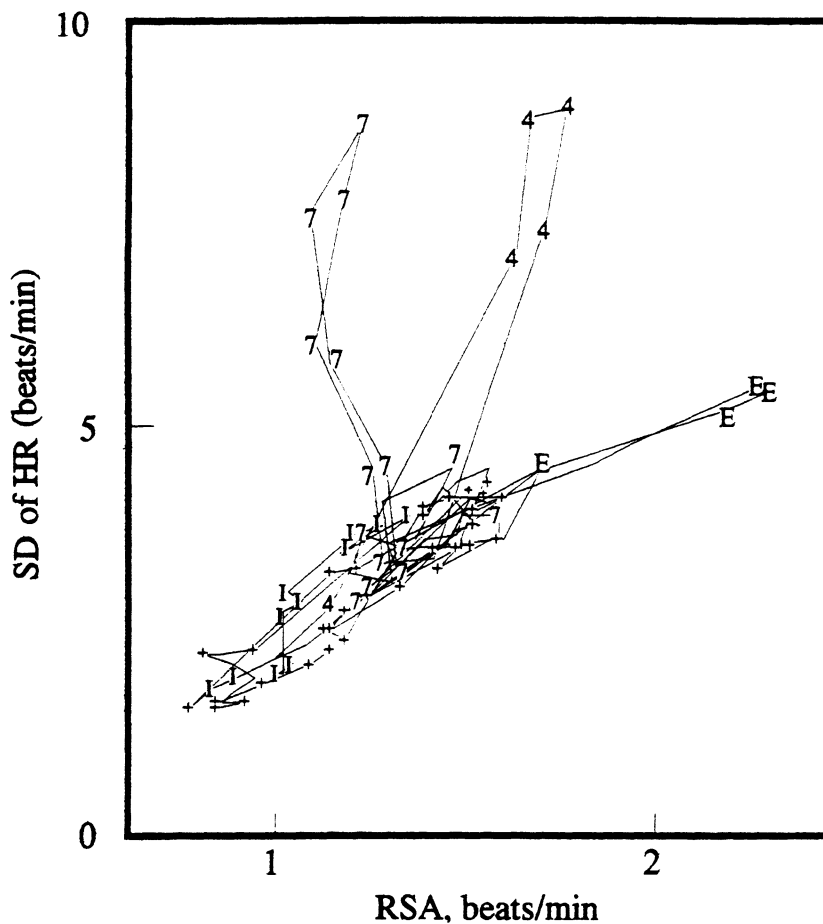


FIG 1. Standard deviation (SD) of heart rate (HR) versus respiratory sinus arrhythmia (RSA) during two different experimental conditions recorded in one subject: 5 minutes of rest: the patient rests quietly during the recording of heart rate (+) or performs deep inspiration (I) or expiration (E); and 5 minutes of a dynamometric test: the subject presses a hand dynamometer at 70% (7) and 40% (4) of maximal strength.

compared with RSA and strongly increased scatter ($R=.31, P<.05$).

Internal consistency of the two variables is shown in Fig 3 for RSA and in Fig 4 for SD: RSA during dynamometry is plotted versus RSA at rest. It can be seen that RSA during the dynamometric part of the experiment correlates highly with RSA in the same volunteer during rest ($R=.88, N=60, P<.001$, Fig 3). For SD (Fig 4), the correlation between dynamometry and rest is not significant ($R=.15, N=60, P=NS$).

Discussion

In this study, the prognostic value of HRV was analyzed from a physiological point of view. Parasympathetic and sympathetic tones are known to influence the total HRV. Although empirical evidence shows a prognostic value of total HRV⁶ measured by SD, a differentiated view of the influences coming from the

ANS holds the promise of a more precise prognostic tool. It also offers possible understanding of the pathophysiological background. It therefore was our aim to

Heart Rate, Respiratory Sinus Arrhythmia, and Intraindividual Standard Deviation of Heart Rate

Parameter	Rest	Dynamometry	P
HR, bpm	65.9±9.73	72.8±10.44	<.001
RSA, bpm	3.01±1.62	2.97±1.30	NS
SD, bpm	5.19±1.98	9.22±3.56	<.001
N	60	60	

HR indicates heart rate; bpm, beats per minute; RSA, respiratory sinus arrhythmia; and SD, standard deviation.

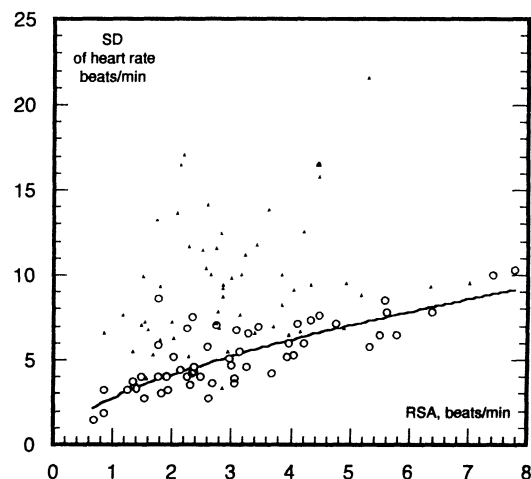


FIG 2. Standard deviation (SD) of heart rate versus respiratory sinus arrhythmia (RSA) during two different experimental conditions: 5 minutes of rest (○): the subjects rest quietly during the recording of heart rate; and 5 minutes of a dynamometric test (▲): the patients press a hand dynamometer at 70% of maximal voluntary contraction force (MVC) for 1 minute and at 40% of MVC for another minute. Heart rate is recorded during contraction and during the adjacent resting phases of 1 minute each. For rest, $SD=2.74 \cdot RSA^{0.584}, R=.78, N=60 (P<.001)$. For dynamometry, $SD=6.46 \cdot RSA^{0.288}, R=.31, N=60 (P<.001)$.

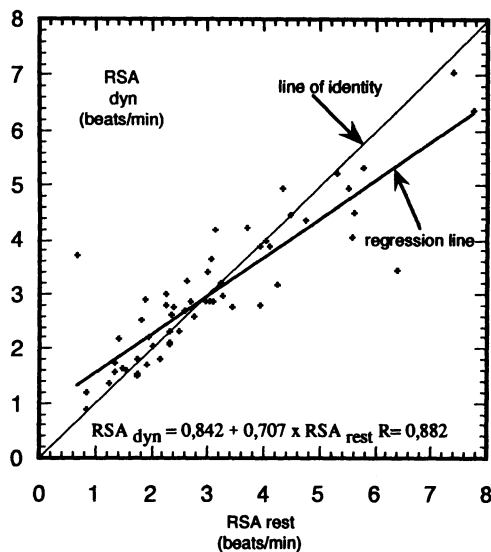


FIG 3. Plot of respiratory sinus arrhythmia (RSA) during dynamometry versus RSA during rest in 60 subjects. Note that the relation is nearly independent of the experimental condition and especially characteristic for a person at low RSA values.

take a look at the two branches of the ANS using SD and RSA.

Healthy subjects were submitted to two simple experimental conditions: rest was used to emphasize parasympathetic tone, whereas sympathetic tone was increased by hand dynamometry. The significant increase of SD and heart rate in the Table indicates enhanced sympathetic drive during hand dynamometry, accompanied by no significant change in RSA.

It is well established that RSA is a measure of parasympathetic (vagal) tone.^{2,5,7} It is less well known which influences constitute the SD of heart rate. Therefore, the correlation between SD and RSA was calculated in Fig 2; a significant positive nonlinear correlation between SD and RSA was found during rest. The

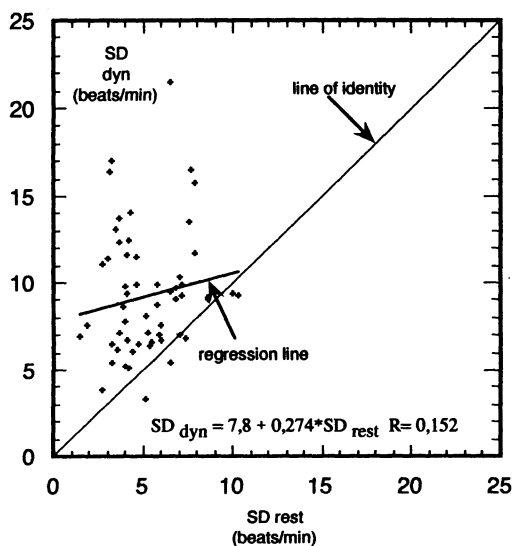


FIG 4. Plot of standard deviation (SD) during dynamometry versus SD during rest in 60 subjects. Note that the quantity is highly dependent on the experimental condition and has a low self-correlation.

scatter present in the correlation indicates that even during rest, SD is not a pure measure of parasympathetic activity. Sympathetic influences therefore are considered to be responsible for the variability in SD. Accordingly, during dynamometry the regression coefficient is significantly reduced compared with rest ($P < .001$) due to the increased sympathetic influences. As shown in the Table, it turned out that RSA was insensitive and SD was highly susceptible to sympathetic effects. Because both sympathetic and parasympathetic effects influence HRV, the SD of heart rate is unable to distinguish between the two effects.

The two branches of the ANS exert a well-established antagonistic influence on the threshold of ventricular fibrillation.¹⁹ Although activation of the sympathetic ANS at every level leads to significant lowering of the threshold for ventricular fibrillation, parasympathetic activity is known to increase this threshold with pre-existing sympathetic arousal.²⁰ Ventricular fibrillation was nearly absent even with ligation of the left anterior descending coronary artery in the absence of sympathetic activity in dogs.²¹ It is also well known that psychological stress accompanied by a high level of circulating adrenergic hormones predisposes to sudden cardiac death.

It has been shown that conditions increasing the parasympathetic tone, such as meditation, are able to reduce premature ventricular beat frequency in cardiac patients.¹⁹ The beneficial effect of vagal stimulation was also found during experimental acute myocardial infarction in which 71% of dogs with vagal stimulation survived after 30 minutes of coronary artery occlusion compared with 10% of the control animals.²²

Therefore, a detrimental effect of sympathetic arousal on ischemic heart muscle can be expected, whereas a cardioprotective effect is ascribed to parasympathetic arousal. Under these circumstances, a strict separation of parasympathetic and sympathetic influences is considered a prerequisite for a prognostic tool. To check the stability of the parameters, the internal consistency was investigated for the RSA (Fig 3) and the SD (Fig 4). RSA proved to be the more stable parameter, being less susceptible to disturbing effects. SD (Fig 4) revealed less stability, showing no significant correlation between dynamometry and rest.

SD of heart rate alone should be used cautiously for prognostic purposes; parasympathetic as well as sympathetic activity will influence SD, and the connection between high values of SD and good prognosis described recently^{6,23} can be expected only if no disturbing sympathetic effect interferes. SD is a measure of the deviation of a parameter around its mean value. If the mean value is the 24-hour heart rate, then its SD is influenced by all variations occurring in the range of seconds to 24 hours. Therefore, a pulse frequency of 70 during the day and 60 during the night without any other variation could produce the same SD as a strong RSA during the day, although the patients' autonomic states could be completely different in the two cases. The amount of circadian variation may be the main factor influencing the 24-hour SD of heart rate.

HRV is a quantity that can be obtained with any Holter ECG. Its obvious clinical importance justifies a careful mathematical analysis separating the influences of the different parts of the ANS. RSA calculated from

mean absolute interval differences is easy to calculate and could complement SD of heart rate. If both SD and RSA are evaluated dynamically from the same data, the sympathetic as well as the parasympathetic part of the HRV can be displayed (Fig 1). These two simple measures of variability offer insights into the tonic state of the ANS during rest as well as into the dynamic variations during exercise. Additional clinical data will have to prove the value of RSA as a prognostic tool in cardiology.

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References

1. Wiersma ED. Der Einfluß von Bewußtseinszuständen auf Puls und die Atmung. *Z Ges Neurol Psych.* 1913;1:24.
2. Fouad FM, Tarazi RC, Ferrario CM, Fighaly S, Alicandri C. Assessment of parasympathetic control of heart rate by a noninvasive method. *Am J Physiol.* 1984;246:H838-H842.
3. Hayano J, Sakakibara Y, Yamada A, Yamada M, Mukai S, Fujinami T, Yokoyama K, Watanabe Y, Takata K. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *Am J Cardiol.* 1991;67:199-204.
4. Billman GE, Dujardin JP. Dynamic changes in cardiac vagal tone as measured by time-series analysis. *Am J Physiol.* 1990;258:H896-H902.
5. Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol.* 1985;249:H867-H875.
6. Casolo GC, Stroder P, Signorini C, Calzolari F, Zucchini M, Balli E, Sulla A, Lazzerini S. Heart rate variability during the acute phase of myocardial infarction. *Circulation.* 1992;85:2073-2079.
7. Hayano J, Sakakibara Y, Yamada A, Yamada M, Mukai S, Fujinami T, Yokoyama K, Watanabe Y, Takata K. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *Am J Cardiol.* 1991;67:199-204.
8. Lombardi F, Sandrone G, Pernpruner S, Sala R, Garimoldi M, Cerutti S, Baselli G, Pagani M, Malliani A. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. *Am J Cardiol.* 1987;60:1239-1245.
9. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerrutti S, Malliani A. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympathovagal interaction in man and conscious dogs. *Circ Res.* 1986;59:176-193.
10. Binkley PF, Nunziata E, Haas GJ, Nelson SD, Cody RJ. Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. *J Am Coll Cardiol.* 1991;18:464-472.
11. Smolander J, Louhevaara V. Effect of heat stress on muscle blood flow during dynamic handgrip exercise. *J Appl Physiol.* 1992;65:215-220.
12. Guzzetti S, Piccaluga E, Casati R, Cerutti S, Lombardi F, Pagani M, Malliani A. Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability. *J Hypertens.* 1988;6:711-771.
13. Hildebrandt G. Chronobiologische Grundlagen der Leistungsfähigkeit und Chronohygiene. In: Hildebrandt G, ed. *Biologische Rhythmen und Arbeit.* Wien/New York: Springer; 1976:1-19.
14. Raschke F. The respiratory system—features of modulation and coordination. In: Haken H, Koepchen HP, eds. *Rhythms in Physiological Systems.* Berlin: Springer; 1991:155-164.
15. Heckmann C, Busch M. Changes in circadian pattern of heart rate in patients after acute myocardial infarction. In: Hildebrandt G, Moog R, Raschke F, eds. *Chronobiology and Chronomedicine.* Frankfurt/Main: Springer; 1987:299-306.
16. Janssen BJA, Tyssen CM, Struyker BHAJ. Modification of circadian blood pressure and heart rate variability by five different antihypertensive agents in spontaneously hypertensive rats. *J Cardiovasc Pharmacol.* 1991;17:494-503.
17. Eckoldt K. Probleme und Ergebnisse der Analyse des Sinusrhythmus. In: Zwiener U, Michalik M, Eckoldt K, Klossek H, eds. *Herzfrequenzvariabilität—Möglichkeiten zur Diagnostik neurologischer Erkrankungen.* Leipzig: Hirzel; 1990:53-63.
18. Kleinbaum DG, Kupper LL. *Applied Regression Analysis and Other Multivariable Methods.* Duxbury, Mass: Duxbury Press; 1978.
19. Lown B, Desilva RA, Reich P, Murawski BJ. Psychophysiological factors in sudden cardiac death. *Am J Psychiatr.* 1980;137:1325-1335.
20. Lown B, Verrier RL. Neural activity and ventricular fibrillation. *N Engl J Med.* 1976;294:1165-1170.
21. Satinsky J, Kosowsky B, Lown B. Ventricular fibrillation induced by hypothalamic stimulation during coronary occlusion. *Circulation.* 1971;93(suppl II):II-60. Abstract.
22. Myers RW, Pearlman AS, Hyman RM, Goldstein RA, Kent KM, Goldstein RE, Epstein SE. Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia. *Circulation.* 1974;49:943-947.
23. Kleiger RE, Miller JP, Bigger JT, Moss AJ, for the Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol.* 1987;57:256-262.