Journal of the American College of Cardiology
© 1999 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 34, No. 1, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00158-8

Physiology

Noninvasive Assessment of the Cardiac Baroreflex: Response to Downward Tilting and Comparison With the Phenylephrine Method

Naohiko Takahashi, MD,* Mikiko Nakagawa, MD,† Tetsunori Saikawa, MD,* Tatsuhiko Ooie, MD, Tadafumi Akimitsu, MD,* Koji Kaneda, MD,* Masahide Hara, MD,* Tetsu Iwao, MD,† Hidetoshi Yonemochi, MD,† Morio Ito, MD,† Toshiie Sakata, MD*

Oita, Japan

OBJECTIVES We studied the relation between changes in systolic blood pressure and RR interval during downward tilting in comparison with assessment of baroreflex sensitivity (BRS) measured by the phenylephrine method (Phe-BRS) and with measures of heart rate variability (HRV).

BACKGROUND The method most extensively used for assessing BRS involves bolus injections of phenylephrine. Several noninvasive methods proposed to assess BRS have not been widely applied in the clinical setting.

METHODS Sixteen healthy male volunteers were studied (mean age ± SD 27.5 ± 4.6 years). Arterial blood pressure using tonometry and electrocardiogram was simultaneously recorded. After 20 min of 70° upright tilting, the table was returned to supine position at a speed of 3.2°/s. Subsequently, BRS was assessed using an intravenous bolus injection of phenylephrine (2 to 3 μg/kg). Heart rate variability under resting conditions also was analyzed.

RESULTS In all subjects, a beat to beat systolic blood pressure increase associated with corresponding RR interval lengthening was observed during downward tilting as well as during phenylephrine administration. During both testing procedures, these two variables showed linear correlation, and the slope of regression line during downward tilting (DT-BRS) correlated significantly with Phe-BRS ($r = 0.79$, $p = 0.0003$). The DT- and Phe-BRS also correlated significantly with the high frequency component of resting HRV ($r = 0.70$, $p = 0.0023$ for DT-BRS; $r = 0.58$, $p = 0.0185$ for Phe-BRS).

CONCLUSIONS We conclude that in a small homogeneous group DT-BRS provided an assessment of reflex cardiac vagal function comparable to that obtained by the phenylephrine method. (J Am Coll Cardiol 1999;34:211–5) © 1999 by the American College of Cardiology

Baroreflex sensitivity (BRS) has been reported to identify patients with increased risk of life-threatening ventricular tachyarrhythmias and sudden death after myocardial infarction (1–5). The method most extensively described for assessing BRS involves bolus intravenous injections of phenylephrine (1–6). The phenylephrine method of BRS assessment (Phe-BRS) has been reported to be safe and well tolerated with no major complications (1–5), but nonetheless requires intravenous administration of the pressor agent. Recently, several noninvasive methods have been proposed for quantifying BRS (7–13). However, they have not been widely applied clinically (14).

The head-up tilt test has been shown to be useful in assessing patients referred for recurrent unexplained syncope. In such testing, we have noted during the return of the table to the supine position from the upright posture a dynamic beat to beat increase in systolic blood pressure in association with an increase in the corresponding RR interval, similar to observations after phenylephrine administration. We therefore hypothesized that assessment of the baroreflex response to the downward tilting (DT-BRS) can serve as a noninvasive index of reflex cardiac vagal function. In the present study, therefore, we compared DT-BRS with Phe-BRS as well as measures of resting heart rate variability (HRV) in healthy young men.

METHODS

Subjects. We studied 16 healthy men (20 to 38-years-old; mean age ± SD 27.5 ± 4.6 years). A detailed medical history and examination excluded the evidence of any organic disease. None of the 16 subjects had a history of vasovagal fainting. None was taking medication and all were

From the *Department of Internal Medicine I, and †Department of Laboratory Medicine, School of Medicine, Oita Medical University, Oita, Japan.

Manuscript received April 28, 1998; revised manuscript received February 9, 1999, accepted March 15, 1999.

JACC Vol. 34, No. 1, 1999
July 1999:211–5

Abbreviations and Acronyms

BRS	=	baroreflex sensitivity
DT-BRS	=	baroreflex sensitivity measured by the downward tilting method
ECG	=	electrocardiogram
HF	=	high frequency (0.15 to 0.45 Hz)
HRV	=	heart rate variability
LF	=	low frequency (0.04 to 0.15 Hz)
Phe-BRS	=	baroreflex sensitivity measured by the phenylephrine method

nonsmokers. Written informed consent was obtained from all subjects. The study was approved by our institution's review board.

Study protocol. All subjects were studied in the fasting state at rest. Studies were performed in a quiet room with dimmed lights between 9 and 11 AM. Each patient was placed on an electrically driven tilt table. A right cubital venous catheter was placed, and arterial blood pressure was recorded noninvasively using tonometry (Jentow-7700, Nihon Colin, Komaki, Japan). The tonometric sensor was attached over the left radial artery. To keep the level of heart and the tonometric sensor equal during tilting, the left arm was held horizontal and supported by a plate secured to the table. The accuracy of continuous blood pressure monitoring using this system has been demonstrated previously (15). Arterial blood pressure and the standard 12-lead electrocardiogram (ECG) were monitored simultaneously, and data were stored in a PCM data recorded (RD-200T, TEAC, Tokyo, Japan). Three-lead precordial Holter ECG recordings (model-459, Del Mar Avionics, Irvine, California) also were obtained throughout the procedure for analysis of HRV.

After waiting 30 min to permit cardiovascular baroreflex mechanisms to achieve a steady state (1,3–5), subjects were asked to breathe at a rate of 15 breaths/min using a metronome, to maximize regularity between the respiratory and the cardiovascular systems. After recording arterial blood pressure and 12-lead ECG for 10 min, passive upward tilting from 0° to 70° was performed and maintained for 20 min. Thereafter, the table was returned to the supine position at a speed of 3.2°/s. Fifteen minutes after completion of downward tilting, at which time the heart rate and blood pressure had returned to steady state levels, BRS was assessed by the phenylephrine method as previously described (6). The drug (2 to 3 μg/kg) was injected over 15 s to obtain a 15- to 40-mm Hg systolic blood pressure increase. Baroreflex sensitivity measured by the phenylephrine method was calculated as the slope of the linear regression line relating systolic blood pressure changes to RR interval changes. Regression lines with more than 20 data points and a correlation coefficient (r) greater than 0.8 were accepted for analysis. The phenylephrine injection was repeated three times and the mean of the three slopes was taken as the BRS value. Baroreflex sensitivity measured by the downward tilting method was calculated as the slope of the linear regression line relating systolic blood pressure changes to RR interval changes during downward tilting. Regression lines with more than 12 data points and r greater than 0.8 were accepted for analysis.

Heart rate variability. Heart rate variability was analyzed using a 300-s interval of Holter ECG recording beginning 10 min after the downward tilting. The power spectrum of the RR intervals was computed by a fast Fourier transform and expressed as the areas under the power spectrum (16).

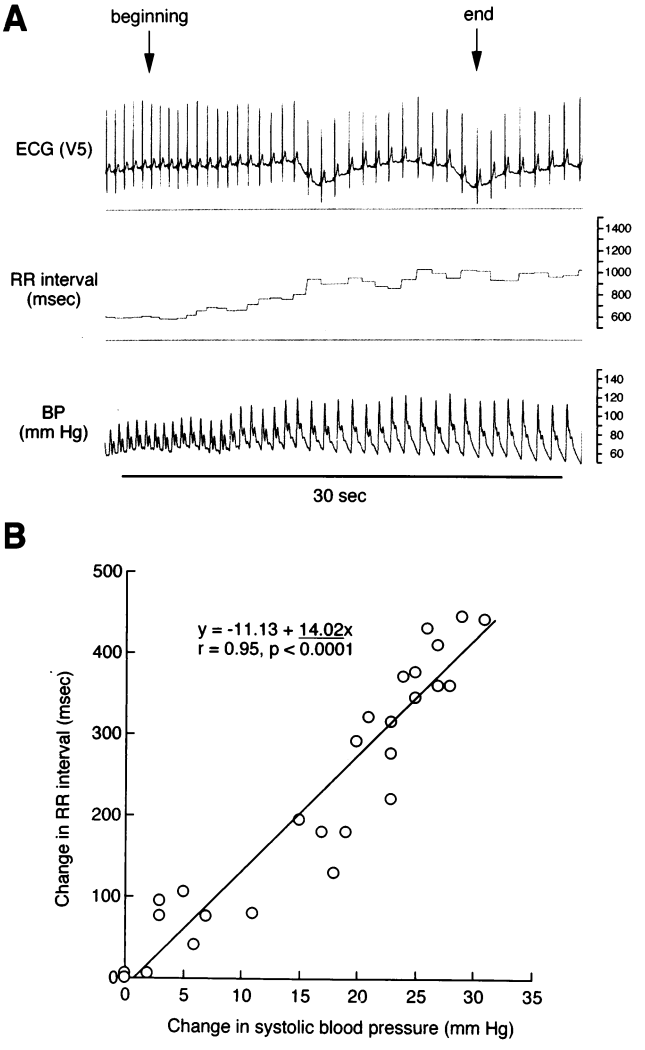

Figure 1. The relation between the changes in systolic blood pressure increase and corresponding RR interval lengthening observed in a 33-year old man during downward tilting. **(A) Top and middle panels:** electrocardiographic tracing of V5 lead and computed RR intervals. **Bottom panel:** arterial blood pressure (BP) recorded with tonometry. **Arrows** indicate the beginning and the end of downward tilting. **(B)** Plotting of corresponding RR interval against systolic blood pressure in this subject revealed a strong correlation ($r = 0.95$; $p < 0.0001$), yielding a baroreflex sensitivity value of 14.0 ms/mm Hg. ECG = electrocardiogram.

We calculated the power of two spectral bands, a low frequency component (LF) at 0.04 to 0.15 Hz and a high frequency component (HF) at 0.15 to 0.40 Hz. The ratio of LF to HF spectra (LF/HF) also was computed. Measured values of HRV were transformed using a natural logarithm because their distributions were skewed.

Statistical analysis. Data are presented as mean value ± SD. Pearson product–moment correlation coefficient was employed to compare how closely two variables were linearly related (17). Correlation coefficients were tested for statistical significance by means of *t* tests. Two correlation coefficients were compared using a test procedure described by Kleinbaum et al. (18). The method of Bland and Altman (19) was used to determine limits of agreement between Phe-BRS and DT-BRS. Limits of agreement were defined as the mean difference in BRS ± 2 SD.

RESULTS

Changes in arterial blood pressure and RR interval during downward tilting. None of the 16 subjects fainted during 20 min of upright tilting. During downward tilting, an increase in systolic blood pressure was observed in all 16 subjects (6 to 30 mm Hg, mean ± SD, 15.1 ± 6.1 mm Hg). A significant linear correlation ($r > 0.8$) was observed between systolic blood pressure increase and corresponding RR interval lengthening in all 16 subjects, as illustrated for a 33-year old man in Figure 1. In this subject, initiation of downward tilting induced a beat to beat increase in systolic blood pressure, reaching maximum approximately 20 s after the beginning of this movement (bottom tracing in Fig. 1A). This increase in systolic blood pressure was accompanied by an increase in the corresponding RR interval (top and middle tracings in Fig. 1A). Plotting of corresponding RR interval against systolic blood pressure in this subject revealed a strong correlation ($r = 0.95$, $p < 0.0001$; Fig. 1B), yielding a DT-BRS value of 14.0 ms/mm Hg. The mean value of DT-BRS in the 16 subjects was 9.9 ± 3.6 ms/mm Hg.

Comparison of DT-BRS with Phe-BRS. In all 16 subjects, intravenous injection of phenylephrine caused a 15- to 40-mm Hg increase in systolic blood pressure showing a significant linear correlation with lengthening of corresponding RR interval. The mean value for Phe-BRS in the 16 subjects was 22.0 ± 10.1 ms/mm Hg. The DT-BRS correlated significantly with Phe-BRS ($r = 0.79$, $p = 0.0003$, Fig. 2). According to the analysis using the Bland-Altman method, the mean difference in BRS as determined by the two methods was 12.0 ms/mm Hg. The limits of agreement were −3.2 to 27.2 ms/mm Hg.

Table 1. Correlation of Baroreflex Sensitivity Measured by the Downward Tilting or Phenylephrine Method With Frequency Domain Analysis of Heart Rate Variability

	r Value	p Value
Downward tilting		
ln HF power	0.70	0.0023
ln LF power	0.41	0.1149
LF/HF	0.08	0.7810
Phenylephrine		
ln HF power	0.58	0.0185
ln LF power	0.32	0.2352
LF/HF	0.08	0.7660

HF = high frequency; LF = low frequency; HF and LF have been log transformed.

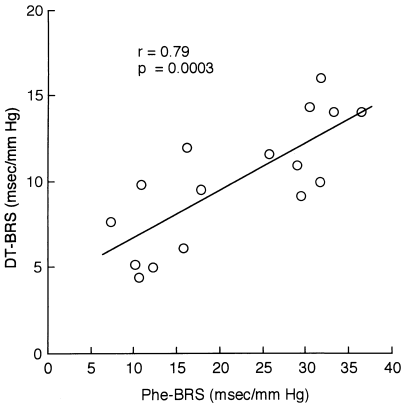

Figure 2. The correlation between baroreflex sensitivity measured by the downward tilting method (DT-BRS) and that by the phenylephrine method (Phe-BRS) in 16 subjects studied; DT-BRS correlated significantly with Phe-BRS ($r = 0.79$; $p = 0.0003$).

Comparison of BRS with HRV. In 16 subjects studied, both DT-BRS and Phe-BRS correlated significantly with the power of HF but not with LF or LF/HF (Table 1).

DISCUSSION

Main findings. In the present study, we demonstrated a strong correlation between systolic blood pressure increase and corresponding RR interval lengthening during downward tilting, which yielded DT-BRS values correlating well with Phe-BRS. The DT-BRS values also correlated significantly with the HF component of resting HRV. Because our present study was conducted in healthy individuals, further investigation will be needed to determine whether this noninvasive method has the same clinical predictive value for major cardiac events as the phenylephrine method.

Previous assessments of BRS. The phenylephrine method has been used extensively for BRS assessment (1–5). The initially required invasive procedure for beat to beat arterial blood pressure measurement has been overcome by the availability of noninvasive methods of pressure monitoring such as use of a Finapres device (14) or tonometry as employed in the present study (15). The remaining disadvantages of the phenylephrine method involve the need for intravenous administration of a pressor agent. Recently, several noninvasive methods to assess BRS have been

advocated (7–13). The Valsalva maneuver and a neck chamber technique have been reported to quantify the baroreflex without using vasoactive drugs (7,8), but the complexities of these techniques and of interpreting the results have discouraged widespread clinical application of these methods (14). Alternatively, spectral techniques have been used to analyze the relationship between spontaneous beat to beat oscillations of blood pressure and RR interval as a way to quantify BRS (9,10). More recently, Hughson and colleagues have advocated a method of studying the spontaneous baroreflex response using sequential beat by beat analysis based on computer scanning of the ECG and continuous noninvasive arterial pressure recordings from a finger (11,12). In this method, a spontaneous baroreflex response was defined as a series of at least three consecutive heart beats in which systolic blood pressure and the subsequent RR interval either both increased or both decreased (11,12). Both spectral analysis and the beat by beat sequence methods are based on the assumption that baroreflexes do not act only to control abrupt changes in arterial blood pressure, but are continuously activated by small variations of systolic arterial pressure. The gain of the spontaneous baroreflex slope observed by these methods, however, indicates minimal recruitment of cardiac vagal efferent neurons by naturally occurring pressure variations. A recent study in which spectral indexes were compared with the phenylephrine method in patients with previous myocardial infarction showed that despite a substantial linear correlation, agreement between the vasoactive drug method and spectral techniques in quantification of BRS was relatively weak (20).

Baroreflex response to downward tilting. Baroreflex mechanisms activated by downward tilting appear more complex than those observed during phenylephrine administration. With the phenylephrine method, a vasoconstriction-induced rise in blood pressure stimulates arterial baroreceptors that cause activation of vagal efferent neurons to result in RR interval lengthening. On the other hand, the rise of blood pressure in response to downward tilting is considered predominantly due to increased venous return followed by an increase in cardiac output; these events necessarily involve activation of cardiopulmonary baroreceptors in addition to arterial baroreceptors. Nevertheless, the significant correlation of DT-BRS with Phe-BRS suggests that the arterial baroreceptors may represent the predominant baroreflex component during downward tilting. Whereas the gain of the phenylephrine-induced baroreflex is an index of the maximum recruitment of cardiac vagal efferent neurons during extremes of parasympathetic engagement by very large pressure increases, baroreflex assessment by downward tilting assesses relatively large but more physiologic levels of recruitment of cardiac vagal efferent neurons. In addition, whereas the phenylephrine test is performed in a resting supine position, downward tilting is initiated from a 70° upright posture in which sympathetic activity is substantially increased (21). Thus, BRS assessment during downward tilting measures baroreceptor sensitivity during a sizable change in sympathetic tone. Resting autonomic function in young, healthy subjects such as those studied here differs from the situation in patients with heart disease, who have substantial increased sympathetic tone that can trigger potentially lethal arrhythmias. Accordingly, the BRS assessment during downward tilting may be more useful than the phenylephrine method because the tilting method evaluates the baroreflex response in the setting of increased sympathetic tone, a physiologic state that is likely in patients with heart disease. Downward tilting does not rely on pharmacologic stimuli and may provide more valuable BRS assessment in patient populations whose reflex cardiac vagal activity requires clinical assessment. Further study is needed to determine whether DT-BRS can provide more useful information than Phe-BRS in patients with heart disease.

Comparison with HRV. In the present study, DT-BRS and Phe-BRS correlated significantly with the power of HF in HRV. Heart rate variability has lacked strong correlation with the Phe-BRS in normal patients (22) and in patients with previous myocardial infarction (4), because measures of HRV primarily reflect tonic vagal activity (4,22). In the present study, HRV was assessed using only a 5-min interval of ECG recording in healthy young men under supine resting conditions. Considerable further study will be needed to clarify the relationship between DT-BRS and measures of HRV in patients with cardiovascular disease.

Study limitations. The present study has several limitations. First, as already mentioned, we tested a relatively small number of male subjects who were young and healthy; Phe-BRS has been shown to correlate negatively with age and to be decreased in patients with organic heart disease (1–5). Prospective evaluation in larger and more varied groups of patients will be necessary to confirm whether DT-BRS generally correlates with Phe-BRS. Second, we assessed DT-BRS only once in each subject; reproducibility and day to day variability of the values obtained should be tested. Third, 70° passive upright tilting maintained for 20 min was chosen, because our protocol was adopted from that used in our department for diagnosis of patients with unexplained syncope. The angle and duration for upright tilting and the speed of downward tilting should be varied to determine the optimal condition for BRS assessment.

Conclusions. We conclude that in a small homogeneous group DT-BRS provided an assessment of reflex cardiac vagal function comparable to that obtained by the phenylephrine method. The downward tilting method is noninvasive and safe, and may show promise for assessment of reflex cardiac vagal activity in some patients with cardiovascular disease.

Acknowledgments

The authors gratefully acknowledge Win K. Shen, MD, Division of Cardiovascular Disease and Internal Medicine, Mayo Clinic, Rochester, Minnesota, for this critical reading and valuable suggestions regarding the manuscript. We thank Miss Emi Noguchi of our department for technical assistance.

Reprint requests and correspondence: Dr. Naohiko Takahashi, Department of Internal Medicine I, School of Medicine, Oita Medical University, 1-1 Idaigaoka, Hasama, Oita 879-5593, Japan. E-mail: takanao@oita-med.ac.jp.

REFERENCES

1. La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. Circulation 1988;78:816–24.
2. Farrell TG, Odemuyiwa O, Bashir Y, et al. Prognostic value of baroreflex sensitivity testing after acute myocardial infarction. Br Heart J 1992;67:129–37.
3. Hohnloser SH, Klingenheben T, van de Loo A, Hablawetz E, Just H, Schwartz PJ. Reflex versus tonic vagal activity as a prognostic parameter in patients with sustained ventricular tachycardia or ventricular fibrillation. Circulation 1994;89:1068–73.
4. De Ferrari GM, Landolina M, Mantica M, Manfredini R, Schwartz PJ, Lotto A. Baroreflex sensitivity, but not heart rate variability, is reduced in patients with life-threatening ventricular arrhythmias long after myocardial infarction. Am Heart J 1995;130:473–80.
5. La Rovere MT, Bigger JT, Jr., Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet 1998;351:478–84.
6. Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man: a quantitative method of assessing baroreflex sensitivity. Circ Res 1969;24:109–22.
7. Airaksinen KE, Hartikainen JE, Niemela MJ, Huikuri HV, Mussalo HM. Valsalva manoeuvre in the assessment of baroreflex sensitivity in patients with coronary artery disease. Eur Heart J 1993;14:1519–23.
8. Ludbrook J, Mancia G, Ferrari A, Zanchetti A. The variable-pressure neck-chamber method for studying the carotid baroreflex in man. Clin Sci Mol Med 1977;53:165–71.
9. Robbe HW, Mulder LJ, Ruddel H, Langewitz WA, Veldman JB, Mulder G. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. Hypertension 1987;10:538–43.
10. Pagani M, Somers V, Furlan R, et al. Changes in autonomic regulation induced by physical training in mild hypertension. Hypertension 1988;12:600–10.
11. Parlow JP, Viale JP, Hughson R, Quintin L. Spontaneous cardiac baroreflex in humans: comparison with drug-induced responses. Hypertension 1995;25:1058–68.
12. Hughson RL, Quintin L, Annat G, Yamamoto Y, Gharib C. Spontaneous baroreflex by sequence and power spectral methods in humans. Clin Physiol 1993;13:663–76.
13. Pellizzer AM, Kamen PW, Jackman G, Brazzale D, Krum H. Non-invasive assessment of baroreflex sensitivity and relation to measures of heart rate variability in man. Clin Exp Pharmacol Physiol 1996;23:621–4.
14. La Rovere MT, Schwartz PJ. Baroreflex sensitivity as a cardiac and arrhythmia mortality risk stratifier. Pacing Clin Electrophysiol 1997;20 part II:2602–13.
15. Sato T, Nishinaga M, Kawamoto A, Ozawa T, Takatsuji H. Accuracy of a continuous blood pressure monitor based on arterial tonometry. Hypertension 1993;21:866–74.
16. Ishida S, Nakagawa M, Fujino T, Yonemochi H, Saikawa T, Ito M. Circadian variation of QT interval dispersion. J Electrocardiol 1997; 30:205–10.
17. Snedecor GW, Cochran WG. Statistical Methods. 7th ed. Ames (IA) Iowa State University Press, 1980:185–7.
18. Kleinbaum DG, Kupper LL, Muller KE. Applied Regression Analysis and Other Multivariable Methods. 2nd ed. Boston: PWS-KENT Publishing, 1988:92–3.
19. Bland JM, Altman DG. Statisitical methods for assessing agreement between two methods of clinical measurements. Lancet 1986;8:307–10.
20. Maestri R, Pinna GD, Mortara A, La Rovere MT, Tavazzi L. Assessing baroreflex sensitivity in post-myocardial infarction patients: comparison of spectral and phenylephrine techniques. J Am Coll Cardiol 1998;31:344–51.
21. Vybiral T, Bryg RJ, Maddens ME, Boden WE. Effect of passive tilt on sympathetic and parasympathetic components of heart rate variability in normal subjects. Am J Cardiol 1989;63:1117–20.
22. Bigger JT, Jr, La Rovere NT, Steinman RC, et al. Comparison of baroreflex sensitivity and heart rate variability after myocardial infarction. J Am Coll Cardiol 1989;14:1511–8.