

Assessment of Baroreceptor Reflex Sensitivity by Means of Spectral Analysis

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SUMMARY A method of determining baroreceptor reflex sensitivity is proposed that is based on spectral analysis of systolic pressure values and RR interval times, namely, the modulus (or gain) in the mid frequency band (0.07–0.14 Hz) between these two signals. Results using this method were highly correlated (0.94; $n = 8$) with results of the phenylephrine method. In addition, compared with the values for the preceding rest period, the modulus decreased during mental challenge, as might be expected from the literature. (Hypertension 10: 538–543, 1987)

KEY WORDS • baroreceptor reflex sensitivity • spectral analysis • phenylephrine • modulus

BARORECEPTOR reflex sensitivity (BRS) is assessed by either the neck suction method¹ or the traditional pharmacological method.^{2,3} In the latter technique a pressor agent (usually phenylephrine) that does not affect heart rate directly is administered as an intravenous bolus injection. The ensuing rise in blood pressure causes a baroreceptor-mediated slowing of heart rate. The successive systolic pressure values are correlated with the length of the next RR interval. The regression coefficient of the correlation diagram gives the BRS in milliseconds of interval prolongation per millimeter of mercury pressure rise (Figure 1).

Variability of blood pressure and RR interval time can be expressed by its standard deviation. However, this measure does not give any information about the source of the fluctuations. In this respect, spectral analysis is more informative, as has been shown for the analysis of heart rate variability^{4,5} and for the rela-

tion between the variations in heart rate and blood pressure.⁶

Recently, Mulder⁶ delineated the potential application of spectral analysis techniques for the assessment of BRS and indicated that the modulus (or gain) of the transfer function between variations in blood pressure and heart rate in the mid frequency band (0.07–0.14 Hz) would be an appropriate quantification of BRS. Thus, the present study 1) assessed BRS with the phenylephrine method and by means of spectral analysis to demonstrate that the modulus in the mid frequency band is an appropriate index of BRS, and 2) compared modulus values during rest and during mental activity to demonstrate that modulus values are sensitive to changes in mental and physiological states, since BRS is thought to decrease during exercise and mental activity⁷ and to peak during sleep.²

Subjects and Methods

Spectral Analysis

Figure 2 shows a series of successive systolic blood pressure values and RR interval times; the corresponding power density spectra are shown in Figure 3. The spectra are normalized so that the total area under each curve equals the variance of the signal divided by the square of the mean.

It is useful to divide the total spectrum into three bands: low frequency band (0.02 to 0.06 Hz), mid frequency band (0.07 to 0.14 Hz), and high frequency band (0.15 to 0.40 Hz). The slow variations (<0.07

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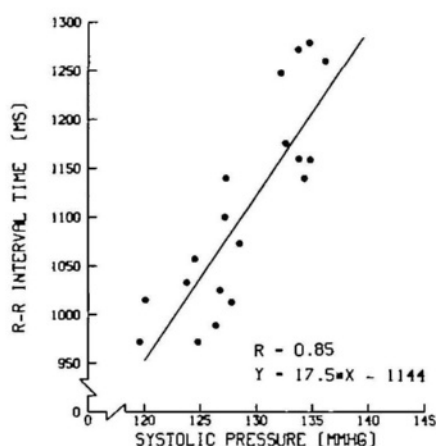


FIGURE 1. RR interval response to arterial pressure elevation caused by intravenous injection of 160 μ g of phenylephrine.

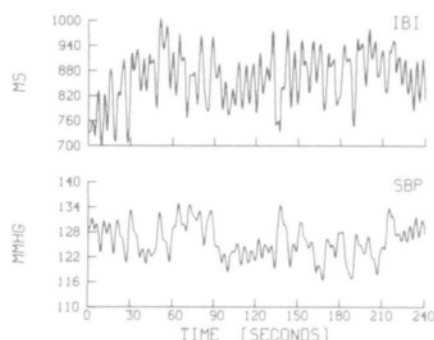


FIGURE 2. Systolic blood pressure (SBP) values and RR interval signals (IBI) during a 4-minute rest period.

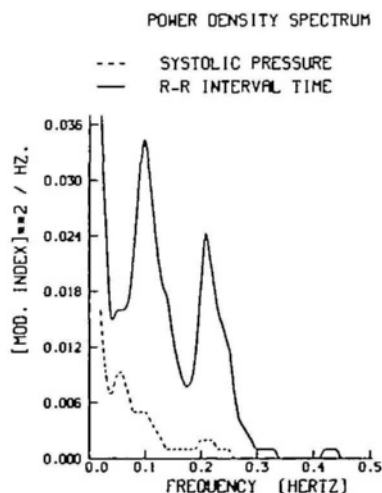


FIGURE 3. Power density spectra of systolic blood pressure values and RR interval signals. Fluctuations are expressed as a fraction of the mean value, and the vertical scale is the squared modulation index \times seconds.

Hz) are supposed to be related to changes in vasomotor tone and, thus, in body temperature or to an adaptation to the task situation, or to both. Variations in the mid frequency band are believed to originate from the characteristics of the blood pressure control system itself.⁸ Variations in the high frequency band can mainly be attributed to respiratory activity (e.g., in Figure 3, the frequency of respiration of that particular subject was 0.23 Hz). Thus, these variations probably are mainly of parasympathetic origin.⁹

The amount of linear coupling between two signals in the frequency domain can be expressed by means of the coherence function. This measure is comparable to the regression coefficient in regression analysis in the time domain, except that it is computed for each frequency region.⁶ Figure 4 shows a characteristic coherence function between systolic blood pressure and RR interval time; the coherence is lowest in the low frequency band and highest in the mid frequency band. To compute a composed coherence measure in a certain frequency band, the weighted coherence of Porges et al.¹⁰ can be used.

An example of a high coherence in the mid frequency band is shown in Figure 5. When systolic blood pressure and RR interval times are both bandpass-filtered (passband of the filter, 0.07–0.14 Hz; i.e., the mid frequency band) the similarities between these filtered signals are far more clear than are those between the raw signals, as depicted in Figure 2.

The modulus, or gain, function specifies the ratio between changes in RR interval time and changes in systolic blood pressure (msec/mm Hg) in a specified frequency band (Figure 6). Therefore the modulus function in the frequency domain is comparable to the regression coefficient in the time domain. The modulus values become unreliable if the coherence is low (similar to the regression coefficient in a regression analysis, which becomes unreliable if the correlation is low).

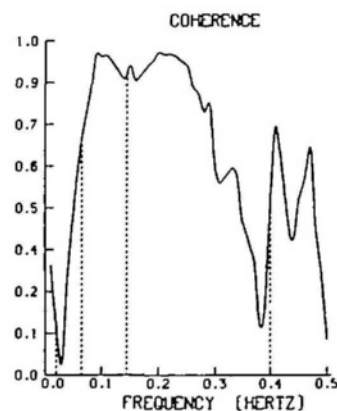


FIGURE 4. Coherence function for the linear relation between systolic pressure and RR interval time. Vertical lines indicate the boundaries of the frequency bands as described in Subjects and Methods.

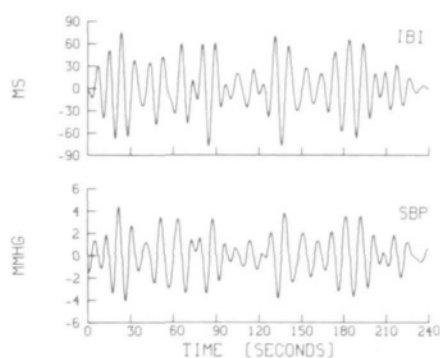


FIGURE 5. The same signals as depicted in Figure 2 except that they are bandpass-filtered (passband, 0.07–0.14 Hz).

Study 1: Phenylephrine Method Compared with Spectral Analysis

Nine men (22–28 years of age) participated in this experiment. All subjects were healthy students or physicians who had given informed consent to participate in this experiment, which was approved by the ethics committee of the University of Bonn. Electrocardiograms were recorded from precordial leads. Arterial blood pressure was measured in the brachial artery by means of an indwelling catheter (diameter 0.9 mm) continuously flushed with physiological saline solution at a rate of 4 ml/hr. A Siemens Elema pressure transducer (Type 746; Erlangen, Federal Republic of Germany) was used. No major complications occurred.

BRS estimated with the phenylephrine method was compared with modulus values in the mid frequency band. In this band, the coherence between the two signals is high and the phase difference (i.e., time lag) relatively stable (about 1.5 seconds).¹¹

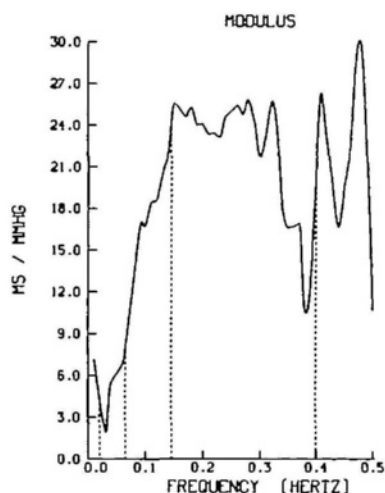


FIGURE 6. Modulus function for the transfer from millimeters of mercury in systolic blood pressure to milliseconds in RR interval time. Vertical lines indicate the boundaries of the frequency bands as described in Subjects and Methods.

Phenylephrine Method

Each subject was subjected to four trials with increasing doses of rapidly injected phenylephrine (20–160 μ g). Doses were chosen in such a way that an ultimate increase in systolic pressure of about 20 mm Hg was obtained. For each subject a mean slope was calculated for the observations used. If the correlation between systolic pressure values and RR interval times had a p value greater than 0.05, the observation was discarded. This procedure is in correspondence to the one used by Smyth et al.² Because all observations of one subject were discarded due to nonsignificant correlations, eight subjects were included in the final analyses.

Spectral Analysis

The modulus values for the same nine subjects were computed from a 5-minute rest period preceding the four administrations of phenylephrine. The first and last 15 seconds were removed from the time series. So all spectral analyses were performed with the CARSPAN program¹² on time segments of 4.5 minutes, which were found to be stationary. The chosen frequency resolution in this cardiovascular spectral analysis program is equal to 0.01 Hz. Therefore, the number of points in the mid frequency band equals nine. From these nine frequency points, only those with a coherence greater than or equal to 0.50 were selected to compute the mean modulus value in this band. This limit of 0.50 was arbitrarily chosen; at this value the proportion of shared variance in both signals is equal to 50%. Also, a composed measure of coherence in the mid frequency band was computed by means of the weighted coherence of Porges et al.¹⁰ All nine frequency points were included in this computation.

Statistical Analysis

Statistical analysis of the difference between the average BRS and modulus values was performed with a two-tailed Student's t test for paired observations. Only eight subjects could be used for these analyses because of the loss of one subject from the phenylephrine method study. The relationship between both methods was analyzed by Pearson's product-moment correlation. Only results with a p level below 0.05 were regarded as significant.

Study 2: Comparison of Modulus Values During Rest and Tasks

Twelve subjects were recruited in a manner identical to that used for the first study. Two mental tasks were used that induce different physiological response patterns. All subjects performed the tasks in the same order, and both tasks were preceded by a rest period. Therefore, the design of this study was Rest 1, Task 1, Rest 2, Task 2.

Task 1: Mental Arithmetic with Noise as Distracting Stressor

The mental arithmetic task was presented as a slide on a screen. The subjects were instructed to add continuously one-digit and two-digit numbers for 5 min-

utes, as fast and as accurately as possible, while being exposed to distracting noise (85 dB). This task leads to an increased heart rate and blood pressure.¹³ A 5-minute rest period preceded the task.

Task 2: Memory Search and Counting

Subjects had to memorize four letters (memory set). After each of 90 stimulus presentations, which consisted of one letter on a screen (interstimulus interval time, 3 seconds), they had to decide whether or not this letter was a member of the memory set. Subjects were asked to respond to targets with their right hand and to non-targets with their left hand. Concurrently, they had also to memorize how many times each letter of the memory set appeared. This task leads to a minor increase in heart rate and blood pressure and to a decrease in the variability of heart rate and blood pressure.¹¹ This 4.5-minute task was again preceded by a 5-minute rest period.

For Task 1 the first minute of the analysis period was removed to attain stationary time series for systolic blood pressure and interbeat interval time. To obtain time segments of equal length for all four conditions, the first and last 30 seconds of both rest periods and the first and last 15 seconds of Task 2 were removed. Thus, all spectral analyses were performed on time segments of 4 minutes.

Statistical Analysis

Statistical analysis of the difference between two means was performed with a one-tailed (for the rest-task comparisons) and a two-tailed (for the comparison of both rests) Student's *t* test for paired observations. The relationship between the modulus values of both rest periods was analyzed by Pearson's product moment-correlation. Only results with a *p* level below 0.05 were regarded as significant.

Results

Study 1

Phenylephrine Method

The average rise in systolic arterial pressure was 19.8 ± 8.6 mm Hg. The average BRS was 16.2 ± 7.3 msec/mm Hg, and the median proportion explained variance (*R*-squared) was 0.68 (range, 0.39–0.86).

Spectral Analysis

The average modulus value of the phenylephrine method for the eight subjects was 18.1 ± 8.9 msec/mm Hg. The median proportion explained variance was 0.80 (range, 0.40–0.95).

The average BRS values, as assessed by both methods, did not differ significantly. A scattergram of the

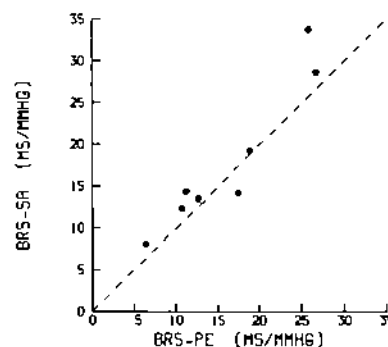


FIGURE 7. Scattergram of paired baroreceptor reflex sensitivities of eight subjects as assessed with the phenylephrine method (BRS-PE) and by means of spectral analysis (BRS-SA). The dashed line is the line of identity.

subjects' scores from both methods is depicted in Figure 7. The correlation between these scores equaled 0.94 ($n = 8$; $p < 0.001$).

Study 2

The amount of linear coupling between systolic blood pressure and RR interval time (i.e., the coherence) remained high during task performance (Table 1). The gain, however, changed; the average modulus values decreased significantly ($p < 0.005$) in comparison with the values obtained during the preceding rest periods (see Table 1). The average modulus values during both rest periods did not differ significantly. A scattergram of the modulus values of all subjects during both rest periods is shown in Figure 8; the correlation between these values equaled 0.92 ($p < 0.0001$).

Discussion

The present results indicate that the modulus in the mid frequency band (0.07–0.14 Hz) between systolic blood pressure and RR interval time gives equivalent results to those obtained using the phenylephrine method. It thus appears to be a useful index for BRS. Furthermore, it has some interesting advantages, which we will point out. The differences in modulus values during mental challenge in Study 2, as compared with the corresponding rest values, show that BRS decreases during mental activity.

One point in Study 1 that needs additional attention concerns the subject in whom the phenylephrine method yielded nonsignificant results four times and who was therefore excluded from further analysis. The highest correlation between systolic blood pressure and interbeat interval time found for this subject was 0.57 ($n = 7$, $p > 0.18$); the corresponding regression

TABLE 1. Average Modulus and Median Coherence Values During Two Resting Periods and Two Stressful Situations

Variable	Rest 1	MA + noise	Rest 2	MS + counting
Modulus (msec/mm Hg)	17.8 ± 9.5	12.6 ± 7.7	16.0 ± 7.3	12.6 ± 6.1
Coherence	0.70 (0.40–0.91)	0.77 (0.61–0.93)	0.77 (0.58–0.93)	0.79 (0.65–0.92)

Modulus values are means \pm SD. Range is shown in parentheses. MA = mental arithmetic; MS = memory search.

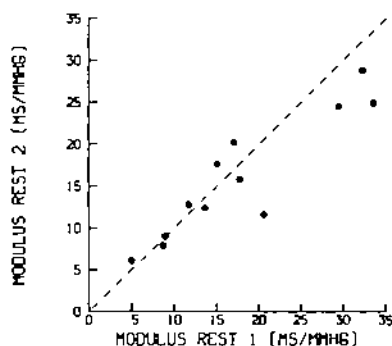


FIGURE 8. Scattergram of paired baroreceptor reflex sensitivities (modulus values) of 12 subjects during two resting periods. The dashed line is the line of identity.

coefficient equaled 27.2 msec/mm Hg. The modulus during the preceding 5-minute rest period for this subject was 27.1 msec/mm Hg; the proportion of explained variance was 0.74. Thus, the spectral analysis technique provided the same BRS as did the phenylephrine method, but only the former method gave a reliable result in terms of proportion of explained variance. One reasonable explanation for the failure of the phenylephrine method could be restriction of range: the highest rise in systolic pressure was 16 mm Hg. This problem, in turn, might be due to the powerful baroreceptor reflex of this subject. A higher dose of phenylephrine might have resulted in a significant correlation.

Another reason for the nonsignificant correlation could be that some interbeat intervals were falling during inspiration. This possibility, however, was not examined. Respiration can be expected to have no impact on the modulus in the mid frequency band because the respiratory frequency is seldom within this band.

The present results indicate that BRS can be estimated by means of spectral analysis. This method probably picks up the same physiological information as does the phenylephrine method in that it describes the cardiac sensitivity to baroreceptor reflex afferents, which is only part of the complete reflex.

Application of spectral analysis techniques has several benefits as well as a few drawbacks as compared with the phenylephrine method. As to its limitations, first, the measuring period should be about 5 minutes in order to obtain reliable results. The phenylephrine method, however, requires only a short measuring time. Second, spectral analysis demands more computing power. The availability of programs (such as CARSPAN) that can be used on personal computers markedly reduce this problem, as the time required to compute spectral densities as well as coherence and modulus functions is only a few minutes. Third, spectral analysis assumes stationary time series. However, in practice this is no problem because the objective of most studies is to determine BRS in a particular situation (i.e., a stationary condition, for example, during sleep, exercise, or mental activity). Such a condition should persist for about 5 minutes for spectral analysis

to be applicable. The cardiovascular system must accommodate itself to the new situation, and time series plots of the signals show that an adaptation period of about 1 minute is usually enough to obtain a stationary situation. This adaptation period should not be included in the analysis. Then, as our experiences confirm, there will be no problems with the assumption of stationary time series.

Clearly, the disadvantages of spectral analysis are not of major importance. The benefits of this method are as follows. First, the injection of phenylephrine and the subsequent rise in blood pressure may not be desirable for some patients. Estimation of the modulus by means of spectral analysis eliminates this problem since it can be derived from spontaneous fluctuations in blood pressure and the corresponding changes in RR interval time. Second, an even more important advantage of the analysis of spontaneous fluctuations is that short-term blood pressure regulation and BRS are not affected by the measuring method itself. Third, repeated injections of phenylephrine should be avoided, whereas spectral analysis of spontaneous fluctuations can be applied repetitively. Fourth, as occurred in this study, the phenylephrine method does not give significant correlations in all subjects, whereas the computation of modulus results in stable and high coherence values.

One implication of these advantages of the spectral analysis technique is that this method could be applied to invasive ambulatory blood pressure monitoring data (as long as the time segments are chosen in such a way that the time series are stationary). This would provide information on BRS under daily living conditions.

Finally, a new method of continuous blood pressure registration should be mentioned. Noninvasive continuous registration of finger arterial blood pressure waveform has been achieved with the Fin.A.Pres method, as described by Settels and Wesseling.¹⁴ (For a comparison of arterial and finger blood pressure measurements, see also Reference 15.) Mulder et al. (unpublished observations, 1987) have shown that when this blood pressure measurement method is used during the same task and rest situation as in Study 2 (memory search and counting), significant changes in BRS, computed by means of spectral analysis, are found. These results suggest that noninvasive assessment of BRS is possible.

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References

1. Eckberg DL, Cavanaugh MS, Mark AL, Abboud FM. A simplified neck suction device for activation of carotid baroreceptors. *J Lab Clin Med* 1975;85:167-173
2. 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;24:109-121
3. Gribbin S, Pickering TG, Sleight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res* 1971;29:424-431
4. Mulder G. The heart of mental effort [Dissertation]. Gronin-

- gen, The Netherlands: University of Groningen, 1980. 216 p
5. Mulder G, Mulder LJM. Information processing and cardiovascular control. *Psychophysiology* 1981;18:392-402
6. Mulder LJM. Model based measures of cardiovascular variability in the time and the frequency domain. In: Orlebeke JF, Mulder G, Van Doornen LJP, eds. *Psychophysiology of cardiovascular control*. New York: Plenum Press, 1985:333-352
7. Sleight P. The physiology of heart-rate control by arterial baroreceptors in man and animals. In: Kitney RI, Rompelman O, eds. *The study of heart-rate variability*. Oxford: Clarendon Press, 1980:107-113
8. Hyndman BW, Kitney RI, Sayers BMCA. Spontaneous rhythms in physiological control systems. *Nature* 1971;233:339-341
9. Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol* 1985;249:867-875
10. Porges SW, Bohrer RE, Cheung MN, Drasgow F, McCabe PM, Keren G. New time-series statistic for detecting rhythmic co-occurrence in the frequency domain: the weighted coherence and its application to psychophysiological research. *Psychol Bull* 1980;88:580-587
11. Veldman JBP, Mulder LJM, Mulder G, Van der Heide D. Short-term coherence between blood pressure and heart rate during mental loading: an exploration in time and frequency domain. In: Orlebeke JF, Mulder G, Van Doornen LJP, eds. *Psychophysiology of cardiovascular control*. New York: Plenum Press, 1985:391-405
12. Mulder LJM, Van Dellen H, Van der Meulen P, Opheikens B. CARSPAN: a spectral analysis program for cardiovascular time series. In: Maarse FJ, Mulder LJM, Sjouw J, Akkerman AE, eds. *Proceedings of the second workshop on computers in psychology*. Lisse: Swets en Zeitlinger, 1987:30-38
13. Neus H, Von Eiff AW. Selected topics in the methodology of stress testing: time course, gender and adaptation. In: Steptoe A, Rüdell H, Neus H, eds. *Clinical and methodological issues in cardiovascular psychophysiology*. Berlin: Springer-Verlag, 1985:78-92
14. Settels JJ, Wesseling KH. Fin.A.Pres: noninvasive finger arterial pressure waveform registration. In: Orlebeke JF, Mulder G, Van Doornen LJP, eds. *Psychophysiology of cardiovascular control*. New York: Plenum Press, 1985:267-283
15. Molhoek GP, Wesseling KH, Settels JJM, et al. Evaluation of the Penáz servo-plethysmo-manometer for the continuous, non-invasive measurement of finger blood pressure. *Basic Res Cardiol* 1984;79:598-609