Spectral analysis of heart rate, arterial pressure, and muscle sympathetic nerve activity in normal humans

AKIO NAKATA,1 SHIGEIO TAKATA,2 TOYOSHI YUASA,1 ATSUHIRO SHIMAKURA,1 MICHIO MARUYAMA,1 HIDEO NAGAI,1 SATORU SAKAGAMI,1 AND KEN-ICHI KOBAYASHI1

1First Department of Internal Medicine and 2Department of Health Science, School of Medicine, Kanazawa University, Kanazawa 920, Japan

Nakata, Akio, Shigeo Takata, Toyoshi Yuasa, Atsuhiro Shimakura, Michio Maruyama, Hideo Nagai, Satoru Sakagami, and Ken-ichi Kobayashi. Spectral analysis of heart rate, arterial pressure, and muscle sympathetic nerve activity in normal humans. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H1211–H1217, 1998.—We investigated the frequency components of fluctuations in heart rate, arterial pressure, respiration, and muscle sympathetic nerve activity (MSNA) in 11 healthy women using an autoregressive model and examined the relationship among variables using Akaike's relative power contribution analysis with multivariate autoregressive model fitting. Power spectral analysis of MSNA revealed two peaks, with low-frequency (LF) and high-frequency (HF) components. The LF component of MSNA was a major determinant of the LF component of arterial pressure and R-R interval variability (0.70 ± 0.07 and 0.18 ± 0.05, respectively). The effect of the LF component of MSNA on arterial pressure showed no change in response to propranolol but was diminished (0.35 ± 0.08) by phentolamine (P < 0.02). The effect of the LF component of MSNA on R-R interval was not altered by pharmacological sympathetic nerve blockade. The HF component of MSNA did not influence other variables but was influenced by R-R interval, arterial pressure, and respiration. These findings indicate that the LF component of MSNA reflects autonomic oscillations, whereas the HF component is passive and influenced by other cardiovascular variables.

multivariate autoregressive model; Akaike's relative power contribution; propranolol; phentolamine

MUSCLE SYMPATHETIC NERVE ACTIVITY (MSNA), which is assessed by direct recording of multiunit sympathetic impulses directed to skeletal muscles, contributes to the regulation of arterial blood pressure by increasing vasoconstrictor tone in the skeletal muscles (7, 25). MSNA consists of pulse synchronous vasoconstrictor impulses and is regulated by arterial and cardiopulmonary baroreceptor mechanisms (10, 11). Thus MSNA discharges show a reciprocal pattern in the response to fluctuations in systemic blood pressure (7, 26). Recordings of MSNA have been used to assess sympathetic nerve activity in patients with various pathophysiological conditions, such as hypertension (4, 14), diabetes mellitus (12), myocardial infarction, and congestive heart failure (17).

Power spectral analysis of the R-R interval and systolic arterial pressure variability is an indirect method of evaluating autonomic nerve activity. However, the relationship among MSNA and the R-R interval and systolic arterial pressure variability has not been clearly demonstrated.

Previous study has quantitatively evaluated MSNA in terms of burst frequency (bursts/min) or burst incidence (bursts/100 heartbeats) (10). This type of quantitative analysis is not adequate for evaluating the relationship of MSNA and the R-R interval and systolic arterial pressure. To clarify this relationship, frequency-domain analysis of MSNA is required.

We investigated the frequency components of fluctuations in the R-R interval, systolic arterial pressure, and MSNA using an autoregressive model analysis and assessed the relationship among variables using Akaike's relative power contribution analysis with multivariate autoregressive model fitting. We also investigated the effect of pharmacological sympathetic nerve blockade with propranolol and phentolamine on spectral components.

METHODS

Subjects

We studied 11 healthy women aged 19–21 yr (mean, 19.8 ± 0.2 yr) in protocol 1 and 5 healthy women and 2 healthy men aged 18–22 yr (20.6 ± 0.5 yr) in protocol 2. The study was approved by our Institutional Ethical Committee, and informed consent was obtained from all subjects. None of the subjects had a history of organic heart disease, hypertension, bronchial asthma, or diabetes mellitus. The mean R-R interval at baseline was 927.1 ± 48.9 ms in protocol 1 and 907.6 ± 53.2 ms in protocol 2. The mean systolic arterial pressure at baseline was 111.0 ± 3.5 mmHg in protocol 1 and 113.4 ± 10.1 mmHg in protocol 2 (Tables 1 and 5).

Recordings of Electrocardiogram, Arterial Pressure, Respiration, and MSNA

A surface electrocardiogram (CMS) was recorded with subjects in the supine position at ambient temperature. Arterial pressure was simultaneously recorded via the brachial artery, and respiratory activity was recorded with a nasal thermistor (Nihon Kohden, Tokyo, Japan). MSNA was recorded as follows: after the peroneal nerve was located by electrical stimulation (1–5 mA), a tungsten microelectrode (FHC, Bowdoinham, ME) with a tip diameter of 1 µm, a shaft diameter of 100 µm, and an impedance of 3–5 MΩ was percutaneously inserted into the muscle nerve fascicle of the peroneal nerve in the popliteal fossa without anesthesia. A surface electrode with a diameter of 10 mm attached to the skin 1–2 cm from the recording electrode was used as the reference electrode (7, 8). MSNA was identified if the Valsalva maneuver enhanced pulse synchronous spontaneous discharges, efferent responses were evoked by tapping on the appropriate muscle but not by gentle skin touch, and no response was evoked by arousal stimulus (7, 10, 13, 15, 16). Spike potentials obtained from the peroneal nerve were fed to a bandpass filter (95.5–5,000 Hz) and were displayed on an oscilloscope and a paper chart recorder as the original neurogram. The original signals were also integrated by a resistance-capacitance circuit (Neuropack 4, Nihon Kohden) with...
a time constant of 0.1 s and were displayed on a paper chart recorder as the mean voltage neurogram (integrated MSNA). The electrocardiogram, arterial pressure, respiration curve, and integrated MSNA were simultaneously stored on a digital audiotape recorder (Sony, Tokyo, Japan).

After 15 min of continuous recording at baseline, propranolol (0.2 mg/kg) was intravenously administered, and data were recorded for an additional 10 min. Phentolamine was then administered at a dose of 10 mg, followed by a 5-mg dose 5 min later, and recordings were again obtained (protocol 1). To clarify whether the changes of parameters after phentolamine were solely the results of a-adrenergic receptor blockade, phentolamine alone was given in an additional seven subjects (protocol 2).

Cardiovascular Variability Signals

Electrocardiogram, arterial pressure, respiratory movement, and MSNA signals were sampled after analog-to-digital conversion at a rate of 250 Hz/channel using a 12-bit converter (GW Instruments, Somerville, MA) and were simultaneously processed on a personal computer to obtain the beat-to-beat variability of the cardiac cycle (R-R interval) and the systolic arterial pressure values (systogram). Respiratory signals were sampled at the peak of the R wave on the electrocardiogram, and MSNA values corresponded to the integrated value of MSNA signals between two consecutive R waves (total burst area per beat).

The beat-to-beat time series of these signals was analyzed using autoregressive spectral analysis to detect the rhythmic components. The model of the order was chosen according to Akaike’s final prediction error (2). The central frequency of each component is expressed in cycles per beat.

Relative Power Contribution Analysis

Akaike’s relative power contribution analysis is a useful method for evaluating feedback controls of various systems based on a multivariate autoregressive modeling approach. This model has been previously described in detail (1). Briefly, k-variate AR model of order M is expressed as

\[ x_i(s) = \sum_{j=1}^{k} \sum_{m=1}^{M} a_{ij}(m)x_j(s-m) + u_i(s) \]

where \( a_{ij}(m) \) is a weighted coefficient and \( u_i(s) \) is white noise. \( P(f) \), the k-k matrix of \( P_{ij}(f) \) [cross-spectral density of \( x_i(s) \) and \( x_j(s) \)] is expressed as

\[ P(f) = \left[ A(A^*) \right]^{-1} \Sigma \left[ (A(f))^{-1} \right]^{-1} \]

where \( \Sigma \) is the k-k matrix of \( \sigma_{ij} \) [the covariance of \( u_i(s) \) and \( u_j(s) \)],

\[ A(f) = \left[ I - \sum_{m=1}^{M} A(m) \exp(-i2\pi fm) \right] \]

where \( A(m) \) is the k-k matrix of \( a_{ij}(m) \), based on the assumption that \( \sigma_{ij} = 0 \) \((i \neq j)\), which yields

\[ p_{ij}(f) = \sum_{j=1}^{k} \left| \left| A(f) \right|^{-1} \right|_{ij}^2 \sigma_{j}^2 \]

where \( \sigma_{ij} \) is the autocovariance of \( u_i(s) \), and

\[ q_{ij}(f) = \left| \left| A(f) \right|^{-1} \right|_{ij}^2 \sigma_{j}^2 \]

where \( q_{ij}(f) \) represents the portion of \( p_{ij}(f) \) originating in the white noise \( u_i(s) \). The relative power contribution of the variable \( x_i \) to the variable \( x_j \) is defined by the following equation

\[ r_{ij}(f) = \frac{q_{ij}(f)}{p_{ii}(f)} \]

A relative power contribution of 0 would indicate that \( x_i \) did not influence \( x_j \), whereas a power contribution of 1 would indicate that \( x_i \) was completely regulated by \( x_j \) at that frequency.

Results were expressed as means ± SE. Data were analyzed by repeated-measures analysis of variance for protocol 1. When a significant difference was observed, a contrast test was used for multiple comparisons. For protocol 2, data were analyzed by Wilcoxon’s signed-rank test. \( P < 0.05 \) was accepted as indicating statistical significance.

RESULTS

Representative Case

Figure 1 shows baseline recordings obtained in a representative subject. The power spectra of the R-R interval and systolic arterial pressure showed two peaks, with a low-frequency (LF) component (0.08 cycles/beat) and a high-frequency (HF) component (0.33 cycles/beat) (Fig. 2). The power spectrum of respiration revealed only one peak. The power spectrum of MSNA showed two peaks, consistent with the spectra of the R-R interval and systolic arterial pressure. The relative power contribution analysis in a representative case is shown in Figs. 3–5.

Mean Group Data

Protocol 1. Propranolol increased the R-R interval (\( P < 0.001 \)) and elevated the systolic arterial pressure (\( P < 0.05 \)) (Table 1). MSNA was the most important contributor to the LF component of R-R interval variability (0.18 ± 0.05) (Table 2). Propranolol tended to inhibit the effect of MSNA on the LF component of the R-R interval (0.06 ± 0.02), but this finding was not statistically significant (\( P = 0.06 \)). Respiration had the greatest effect on the HF component of the R-R interval variability (0.43 ± 0.08), and its effect was not influenced by pharmacological sympathetic nerve blockade.

The LF component of systolic arterial pressure variability was significantly influenced by MSNA (0.70 ± 0.07) (Table 3). This effect of MSNA was not altered by propranolol but was inhibited by phentolamine (0.35 ± 0.08) (\( P < 0.01 \)). The major contributor to HF of systolic arterial pressure variability was respiration, and pharmacological sympathetic nerve blockade did not alter this effect.

The LF component of MSNA was not significantly influenced by the R-R interval, systolic arterial pressure, or respiration. The HF component was influenced by the R-R interval (0.15 ± 0.03), systolic arterial pressure (0.07 ± 0.02), and respiration (0.20 ± 0.06) (Table 4). Pharmacological sympathetic nerve blockade did not alter the HF findings.
Protocol 2. To determine whether the changes of parameters after phentolamine were solely the results of α-adrenergic receptor blockade, phentolamine alone was given in an additional seven subjects. The results are shown in Table 5. After the administration of phentolamine alone, R-R interval shortened (907 ± 53.2 vs. 788.6 ± 56.1 ms, P < 0.02, respectively), systolic arterial pressure diminished (113.4 ± 10.1 vs. 107.7 ±
8.8 mmHg, \( P < 0.05 \), respectively), and the influence of MSNA on the LF component of systolic arterial pressure variability decreased (0.64 ± 0.08 vs. 0.20 ± 0.09, \( P < 0.02 \), respectively). The change of the influence of MSNA on R-R interval variability was not statistically significant, so the reduction of the influence of MSNA on the LF component of MSNA in protocol 1 was considered to be solely the effect of \( \alpha \)-adrenergic receptor blockade.

**DISCUSSION**

Spectral analysis breaks down the stochastic process into its sinusoidal components. Power spectral analysis of the R-R interval and systolic arterial pressure variability is a widely accepted method for indirect evaluation of autonomic nervous activity. However, the mechanisms responsible for these oscillations, especially the LF component, are not fully understood. The HF component of R-R interval variability is believed to reflect vagal activity, and the LF oscillation of R-R interval variability is believed to be regulated by both sympathetic and vagal nerve activity (3, 21). The LF oscillation of arterial pressure variability (i.e., Mayer waves) decreases after \( \alpha \)-sympathetic nerve blockade, suggesting that it reflects sympathetic nerve activity, although the precise mechanisms have not been identified (22). Direct recording of MSNA may help to identify these mechanisms.

Previous studies have quantified MSNA in terms of the burst frequency or burst incidence. However, studies using these parameters have shown no clear relationship between MSNA and the R-R interval and systolic arterial pressure variability. Frequency-domain analysis of MSNA is required to examine this relationship.
Because burst frequency and burst incidence are not suitable for frequency-domain analysis, we used the integrated value of MSNA (total burst area per beat).

A previous study has reported that the frequency components of MSNA were ~0.1 and 0.25 Hz, which were consistent with the frequency components of the R-R interval and mean arterial pressure spectra (9, 10, 20, 23, 24, 27). Sugiyama et al. (24) have observed a linear correlation between the mean arterial pressure and MSNA, assessed by coherence analysis, at frequencies of 0.1 and 0.25 Hz. Montano et al. (18) have found that the LF component of R-R interval variability correlated with measurements of sympathetic discharge recorded from fibers isolated from a thoracic sympathetic outflow largely contributing to cardiac innervation. However, Saul et al. (23) have found no correlation between spectral measurements of R-R interval variability and MSNA at baseline. MSNA correlated significantly with the LF component of R-R interval variability in humans only during nitroprusside infusion, which is associated with reflex sympathetic activation (23).

Cross-spectral and coherence analyses, which are used to estimate the frequency response function, are of limited usefulness for the analysis of data obtained from feedback systems. With coherence analysis, the closed-loop circuit of the feedback system must be interrupted and the input activity changed to white noise. However, such maneuvers cannot be applied in human studies. The interactions among R-R interval, systolic arterial pressure, and MSNA are regulated by feedback systems (5, 6). An increase in MSNA raises arterial pressure, and an increase in arterial pressure suppresses MSNA via an arterial baroreflex mechanism. Akaike's relative contribution analysis makes it possible to analyze the interaction among these feedback systems during normal human activity and to demonstrate the direction of the effect (19).

In the present study, spectral analysis with autoregressive modeling showed that the spectral characteristics of MSNA, like the R-R interval and systolic arterial pressure spectra, had periodic structures, which is consistent with previous studies (20, 24). Akaike's power contribution analysis showed that the LF component of systolic arterial pressure was influenced by the LF component of MSNA. However, the LF of MSNA had a smaller effect on the R-R interval than on systolic arterial pressure. The LF component of MSNA was not

---

**Table 1. Effect of propranolol and phentolamine on R-R interval and systolic arterial pressure**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Propranolol</th>
<th>Phentolamine</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-R interval, ms</td>
<td>927.1 ± 48.9</td>
<td>1,082.7 ± 47.4*</td>
<td>965.4 ± 45.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic arterial pressure, mmHg</td>
<td>111.0 ± 3.5</td>
<td>115.9 ± 3.8†</td>
<td>107.1 ± 3.8</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Values are means ± SE. P values were calculated using analysis of variance. *P < 0.001 compared with baseline by contrast test. †P < 0.05 compared with baseline by contrast test.

---

**Table 2. Influences of systolic arterial pressure, respiration, and MSNA on R-R interval variability determined by Akaike's relative power contribution analysis**

<table>
<thead>
<tr>
<th>Components</th>
<th>Factors</th>
<th>Baseline</th>
<th>Propranolol</th>
<th>Phentolamine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF</td>
<td>SAP</td>
<td>0.00 ± 0.00</td>
<td>0.01 ± 0.00</td>
<td>0.01 ± 0.00</td>
<td>NS</td>
</tr>
<tr>
<td>LF</td>
<td>Respiration</td>
<td>0.06 ± 0.01</td>
<td>0.08 ± 0.02</td>
<td>0.07 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>LF</td>
<td>MSNA</td>
<td>0.18 ± 0.05</td>
<td>0.06 ± 0.02</td>
<td>0.08 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>HF</td>
<td>SAP</td>
<td>0.14 ± 0.06</td>
<td>0.03 ± 0.01</td>
<td>0.19 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>HF</td>
<td>Respiration</td>
<td>0.43 ± 0.08</td>
<td>0.38 ± 0.07</td>
<td>0.53 ± 0.07</td>
<td>NS</td>
</tr>
<tr>
<td>HF</td>
<td>MSNA</td>
<td>0.02 ± 0.01</td>
<td>0.03 ± 0.01</td>
<td>0.03 ± 0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. SAP, systolic arterial pressure; LF, low frequency; HF, high frequency; MSNA, muscle sympathetic nerve activity. NS, not significant. P values were calculated using analysis of variance.
Akaike’s relative power contribution analysis

Influences of R-R interval, systolic arterial pressure, and respiration on MSNA determined by Akaike’s relative power contribution analysis

Table 3. Influences of R-R interval, respiration, and MSNA on systolic arterial pressure variability determined by Akaike’s relative power contribution analysis

<table>
<thead>
<tr>
<th>Components</th>
<th>Factors</th>
<th>Baseline</th>
<th>Propranolol</th>
<th>Phentolamine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF</td>
<td>R-R interval 0.08 ± 0.03 0.13 ± 0.03 0.20 ± 0.07 NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>Respiration 0.04 ± 0.02 0.04 ± 0.01 0.04 ± 0.02 NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>MSNA 0.70 ± 0.07 0.61 ± 0.08 0.35 ± 0.08* &lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>R-R interval 0.18 ± 0.06 0.20 ± 0.05 0.12 ± 0.05 NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>Respiration 0.50 ± 0.07 0.50 ± 0.07 0.50 ± 0.07 NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>MSNA 0.02 ± 0.01 0.03 ± 0.01 0.02 ± 0.01 NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. Definitions are as in Table 2. P values were calculated using analysis of variance. *P < 0.01 compared with baseline by contrast test.

Influenced by the R-R interval, systolic arterial pressure, or respiration, but the HF component of MSNA was influenced by the R-R interval, systolic arterial pressure, and respiration. These findings suggest that the LF component of MSNA represents autonomic oscillation, whereas the HF component is passive. The HF component of MSNA did not influence other variables.

Effects of Pharmacological Sympathetic Nerve Blockade

Intravenous administration of propranolol tended to inhibit the influence of MSNA on the LF component of the R-R interval but did not alter the effect of MSNA on the LF component of systolic arterial pressure variability. Phentolamine reduced the relative power contribution of MSNA to the LF component of systolic arterial pressure variability. Previous studies have shown that phentolamine reduces the power of the LF component of the R-R interval and arterial pressure variability (22). Thus the inhibitory effect of phentolamine on the influence of MSNA on the LF component of systolic arterial pressure variability may be greater than the phentolamine-induced reduction of the relative power contribution.

In conclusion, spectral analysis of MSNA revealed that MSNA variability was composed of LF and HF oscillations. The LF component of MSNA appeared to reflect autonomic oscillation, whereas the HF component of MSNA appeared to reflect passive oscillation and was affected by the R-R interval, systolic arterial pressure, and respiration. The LF of MSNA regulated the LF of R-R interval and systolic arterial pressure variability, although it had a greater influence on systolic arterial pressure than on the R-R interval. Multivariate autoregressive model fitting appeared to be a useful approach for investigating the dynamic interactions among the R-R interval, systolic arterial pressure, respiration, and MSNA.

We thank The Institute of Statistical Mathematics for providing the program package TISMAC, Prof. Y. Tamura for giving helpful advice on the mathematics, and Prof. T. Mano for invaluable help with the development of the microneurographic technique in our department.

Address for reprint requests: A. Nakata, First Department of Internal Medicine, School of Medicine, Kanazawa University, Takaramachi 13-1, Kanazawa 920, Japan.

Received 11 August 1997; accepted in final form 30 December 1997.

Table 5. Effect of phentolamine alone in R-R interval, systolic arterial pressure, influences of MSNA to R-R and SAP variability

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Phentolamine</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-R interval, ms</td>
<td>907.6 ± 53.2</td>
<td>788.6 ± 56.1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Systolic arterial pressure, mmHg</td>
<td>113.4 ± 10.1</td>
<td>107.7 ± 8.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Influence of MSNA on R-R variability (LF)</td>
<td>0.14 ± 0.06</td>
<td>0.07 ± 0.02 NS</td>
<td></td>
</tr>
<tr>
<td>Influence of MSNA on SAP variability (LF)</td>
<td>0.64 ± 0.08</td>
<td>0.20 ± 0.09 &lt;0.02</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. Definitions are as in Table 2. P values were calculated using analysis of variance. *P < 0.01 compared with baseline by contrast test.
REFERENCES


