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*Am J Physiol Heart Circ Physiol* 288:504-510, 2005. First published Sep 23, 2004;
doi:10.1152/ajpheart.00366.2004

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# Phase-averaged characterization of respiratory sinus arrhythmia pattern

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Submitted 26 April 2004; accepted in final form 15 September 2004

**Gilad, O., C. A. Swenne, L. R. Davrath, and S. Akselrod.** Phase-averaged characterization of respiratory sinus arrhythmia pattern. *Am J Physiol Heart Circ Physiol* 288: H504–H510, 2005. First published September 23, 2004; doi:10.1152/ajpheart.00366.2004.—A method for the accurate time-domain characterization of respiratory sinus arrhythmia (RSA) pattern is presented and applied to two groups of healthy subjects to lay the baseline of RSA patterns and to underlay their features: response to standing, stability in successive recordings, and individuality of the shape of RSA pattern. RSA pattern is evaluated by selective averaging of heart rate (HR) changes from multiple respiratory cycles over the respiratory phase and represents the complete modulating function of HR by respiration. The RSA pattern is evaluated with free respiration and even in cases of severe arrhythmia. Estimation error is 6–8% in magnitude, phase resolution is 0.2 rad, and sensitivity margin for respiratory-related HR variability (HRV) components is 1%. RSA magnitude, phase lag, and expiration-to-inspiration time ratio are derived in addition to the entire pattern. In a group of 10 healthy young adults, a phase lag difference of 11.4 ± 8.5% (mean ± SD, $P < 0.004$) was observed between supine and standing postures, possibly ascribed to breathing mechanics. A second group of 15 healthy young adults at supine rest showed stability of the RSA pattern in successive recordings (several weeks apart) as well as individuality among subjects. This may suggest a nonscalar individual long-term index for cardiorespiratory coupling. The method is complementary to the existing statistical and spectral methods. It allows the complete characterization of the primary RSA components and may provide new insight into the effects of vagal activity and changes in clinical conditions.

autonomic function; heart rate variability; integral pulse frequency modulation; modulating function

RESPIRATORY SINUS ARRHYTHMIA (RSA) is a strong modulatory effect of heart rate (HR) by respiration (4). It is widely accepted that RSA is essentially mediated by vagal parasympathetic activity (22). The mechanism of HR modulation by respiration has been ascribed to a central medullary "clock" mechanism and is strongly affected by the baroreflex. Blood pressure changes, induced by respiration mechanics, are sensed by the baroreceptors that influence central autonomic HR modulators (15, 20). Another approach to the origin of RSA suggests that RSA is maximizing oxygen saturation as part of a control mechanism responsible for gas consumption efficiency (Ref. 11; R. Langer, unpublished observations). Afferent stimuli from stretch receptors in the lungs and thoracic wall may also contribute to RSA coupling (9, 20, 25) along with the inspiratory vagal inhibition.

Previous studies describe the RSA coupling mathematically with a transfer function (22) and as an integral pulse frequency modulation model (3). RSA magnitude estimation is widely used as an index of cardiac vagal activity, which is one of the main components of HR variability (HRV). RSA is also related to the high-frequency (HF) peak in the HRV spectrum. Common techniques for measuring RSA include time-domain (12, 17, 21, 24) and frequency-domain (1, 2, 12, 18) methods. The latter estimates the HF component magnitude and phase from the HRV spectrum.

Several recent studies suggest a third approach for describing the time-domain RSA with respect to the respiratory phase (7, 16, 19) (also known as "phase-domain" approach, respiration response curve, or RSA phase pattern). We chose the short-term RSA pattern and used it throughout this study. This approach is based on averaging R-R interval deviations along several respiratory cycles triggered by the respiratory phase. The result is the dynamic pattern of R-R interval change along the respiratory cycle. Several researchers have applied the method to investigating magnitude (5, 23, 25, 27) and phase properties (5, 14, 17, 25, 26) of RSA.

The aim of this work is to enhance the phase-domain approach and to provide a complete characterization of the modulating function. We improve the previous implementations by introducing the concept of "selective" integration.

We perform an accurate characterization of the exact HR changes along the phase of the respiratory cycle, using a statistical approach for the selective integration of multiple respiration cycles. The RSA pattern for each respiratory cycle is evaluated by interpolating the deviations of R-R intervals with cubic spline and scaling each respiratory cycle into $2\pi$ radians. Outliers are removed by applying an iterative process to select a certain percentage (normally 80%) of the respiratory cycles. The selected 80% of respiratory cycles are a cluster of the most similar RSA patterns among the entire set and are averaged to generate the typical RSA pattern of the specific record (Avg80 method).

Two groups of healthy normal subjects were studied to lay the baseline of RSA patterns. In addition, we compared the results of our method with two previous algorithms using averaging of 100% of respiration cycles (Avg100 method; Ref. 16) or taking the median value of the interpolated R-R interval for each respiration phase (Med100 method; Ref. 7).

## METHODS

### *Subjects and Data Acquisition*

The baseline RSA pattern was investigated in two normal groups. In *group 1* the effect of posture (supine rest and standing) was recorded, whereas in *group 2* the effect of long-term consistency between repeated supine sessions several weeks apart was recorded.

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*Group 1. Group 1* was the first normal group and included 10 healthy subjects (*YN1–YN10*), 4 men and 6 women, age 24–37 yr (mean ± SD: 29.0 ± 4.1 yr). This data set is a control group taken from a previous study by our group (6). The Institutional Review Board of Tel Aviv University approved this study, and all subjects signed a written informed consent form.

Signals were sampled simultaneously at 500 Hz with a Biopac multichannel device and Acknowledge software (MP100-Biopac system). ECG (leads I and II) was recorded along with the respiratory signal (Respitrace pneumoplethysmograph rib and abdomen impedance belts). The Respitrace measures a voltage proportional to chest cage contour. Breathing rate and depth were spontaneous.

The protocol included 30-min quiet, supine rest followed by several autonomic stimuli, among which was active change in posture from supine to standing and 5-min recording in a standing posture. For the purposes of our RSA pattern study, we used a supine rest session and a standing session. We ignored the first 5 min of the supine session and the first minute after transition to standing to obtain steady-state recordings. The purpose of this data set was to demonstrate the differences of RSA patterns between postures.

*Group 2. Group 2* was the second normal group and included 15 healthy male subjects (*TN1–TN15*), age 21.9–34.6 yr (mean ± SD: 25.9 ± 3.7 yr). This data set was taken from a study on improvement of baroreflex sensitivity by sensory stimulation to the feet (assumed not to affect RSA pattern estimation) (10). The Leiden University Medical Center Ethics Review Committee approved the protocol of this study, and all subjects signed a written informed consent form.

ECG (leads I, II, and $V_3$) was recorded at 500 Hz, along with two extra electrodes applied to the lateral sides of the thorax to monitor respiration (impedance method). The protocol included 60 min of supine rest in three measurement sessions, *A*, *B*, and *C*. *Session B* was 1 day after *session A*, and *session C* was several weeks later. Sensory stimulation was applied to both feet in *sessions A* and *B* but not in *session C*. The purpose of this data set was to demonstrate the consistency of the RSA pattern over several weeks as well as the individual differences among subjects.

### *Extracting RSA Pattern*

QRS complex was detected from lead II with a threshold and manual correction method followed by a squared interpolation to refine time estimation. Time series representing the onset of expiration were extracted from the respiratory signals by a similar procedure. A triangular window smoothing filter was applied before detection. The onset of expiration is represented by maxima in *group 1* and by minima in *group 2* because of the different devices used. Poor respiratory signal quality in some of the *group 2* recordings (impedance method) reduced the number of reliable recordings for analysis from 15 to 7. Signal processing and analysis were implemented with Matlab (Mathworks) routines.

Calculation of the RSA pattern from a set of $m$ respiratory cycles was initiated by cubic spline interpolation of the R-R intervals into $n = 50$ data points for each of the $m$ respiratory cycles (variability in respiration time $T$ is compensated by different sampling times equal to $T/n$). The $n$ points for all $m$ cycles correspond to $2\pi$ and are drawn and displayed superimposed upon each other (Fig. 1).

An iterative process was used to calculate the average RSA pattern of 80% of the respiratory cycles, after 20% outliers were removed. Let $x_{ij}$ represent a sample of the $i$th interpolated point of the $j$th respiration cycle, where $i = 1, \ldots n$ and $j = 1, \ldots m$. The algorithm uses $k$ iterations, where the iteration number is marked as a superscript. The algorithm starts by calculating the initial average RSA pattern $\overline{x^0}$ and the phase $\overline{\phi^0}$ of its maximum value, where $\overline{x_i^0} = {}^1\!/_m \sum_{j=1}^{m} x_{ij}$. For each of the $m$ respiration cycles, the variance $V_j$ from $\overline{x^0}$ and the phase difference $\Delta\phi_j = |\overline{\phi^0} - \phi_j|$ are evaluated, where $V_j = \sum_{i=1}^{n} (\overline{x_i^0} - x_{ij})^2$ and $\phi_j$ is the phase of the $j$th respiration cycle maximal value.

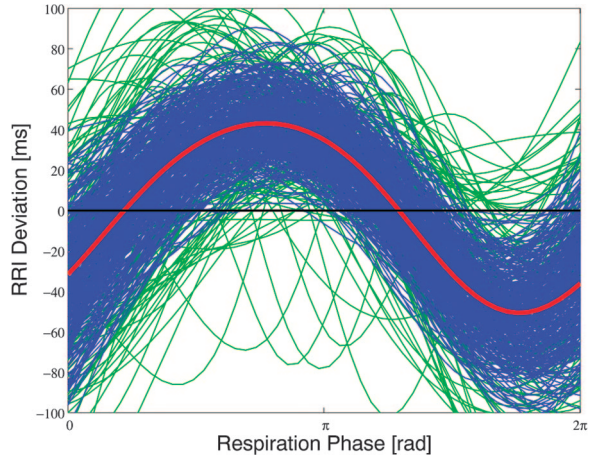


Fig. 1. Result of last iteration for evaluation of respiratory sinus arrhythmia (RSA) pattern (*subject YN1* at supine rest) showing the cluster containing 80% of respiratory cycles (blue), its average representing the primary RSA pattern (red), and the 20% outliers (green). RRI, R-R interval.

From the $m$ values of $V_j$ and $\Delta\phi_j$, a subset $\{s^1\}$ is selected to include $0.9m$ smallest values for $V_j$ followed by a selection of $0.8m$ smallest values for $\Delta\phi_j$. The two-stage selection is performed serially. This subset marks the 80% of the respiration cycles that are similar to the average RSA pattern in terms of variance and maxima location. New average RSA pattern and phase $\overline{x^1}$ and $\overline{\phi^1}$ are calculated with the subset $\{s^1\}$, where $\overline{x_i^1} = {}^1\!/_{0.8m} \sum_{j \in \{s\}} x_{ij}$, $i = 1, \ldots n$.

The algorithm performs $k$ iterations for convergence into a fixed subset $\{s^k\}$, which defines the final RSA pattern $\overline{x^k}$ and the phase of the maximum $\overline{\phi^k}$. In each iteration after the first one, the mean RSA pattern is evaluated by averaging the remaining 80% from the previous iteration and 20% outliers are evaluated again from the total 100% cycles. Up to $k = 6$ (typically 3 or 4) iterations are required before convergence is reached. The final subset $\{s^k\}$, 20% outliers, and final RSA pattern are displayed in Fig. 1. We define the peak-to-peak magnitude of the final RSA pattern as $P \equiv \max\overline{x^k} - \min\overline{x^k}$, the phase of the maximal value $\phi^{max} \equiv \overline{\phi^k}$, and the phase of the minimal value $\phi^{min}$. The 20% outliers can be related to any nonstationary behavior of the heart-lung system such as low-frequency components, HR arrhythmia, or simply very long breaths, instant breathing interruption, or saliva swallowing.

### *Accuracy of Estimated RSA Pattern*

The accuracy of the RSA pattern can be characterized by three different parameters, namely, the vertical standard error, the horizontal phase resolution, and the sensitivity to respiration-related components. Standard error of the selected 80% was estimated along the final RSA pattern (Fig. 2). Typical values for the vertical standard error were 6–8% of the RSA pattern magnitude (peak to peak) for 30- and 60-min records and 15–24% for 5- and 10-min records.

Horizontal phase resolution is mainly bounded by the low bandwidth of the respiratory signals, resulting in a smearing effect when attempting to phase lock multiple cycles. This will limit the phase resolution to 0.2 rad. Phase resolution was taken as the inverse of the maximal first derivative of the RSA pattern (phase "rise time"). In our two normal data sets, the measured phase resolution was in the order of 1.0 rad. Measurement done on a third data set of humans after heart transplant gave a phase resolution of 0.5 rad. Therefore, we conclude that the practical horizontal resolution observed in our data is the true physiological variation rate because the method resolution will allow changes five times faster to be observed (up to the 0.2-rad limit).

RSA pattern is only sensitive to respiration-related components of HRV. Frequency components of HRV that are not related and therefore phase locked to the respiration period will vanish throughout the

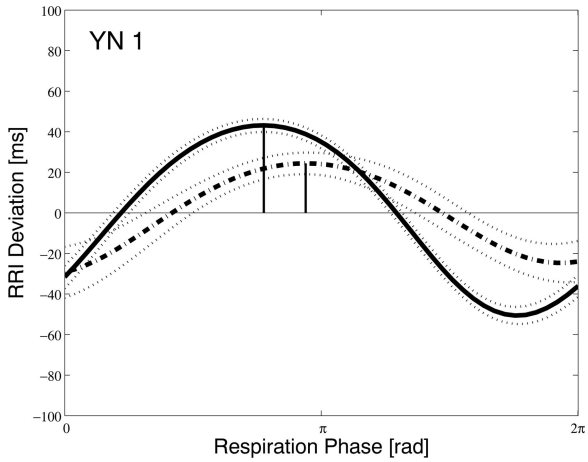


Fig. 2. RSA pattern of normal *subject YN1* (*group 1*) at supine rest (solid line) and standing posture (dash-dot line). Standard error estimation is shown around each curve (dotted lines). Magnitude and phase differences are clearly seen (vertical lines). Origin is the onset of expiration.

integration process. For a typical 5-min recording, the presence of nonrespiratory HRV components, different by >1% from the respiration rate, will not affect the resulting RSA pattern because these will vanish with averaging.

### *Comparison to Previous Methods*

The RSA pattern estimated by our method for 20% outlier removal was compared with estimation by two previously published methods. The first method (Avg100) simply averages 100% of the respiration cycle without considering outliers (16). The second method (Med100) is calculation of the median value from 100% of the *m* respiration cycles. This is done separately for each of the *n* respiration phase positions (7).

The comparison was quantified by taking the SD of the difference between our method (Avg80 $\equiv \overline{x^k}$) and the two previous methods (Avg100 and Med100). This was taken in percentage units relative to P/2, half of the peak-to-peak RSA magnitude measured with our method (Avg80), and was referred throughout this study as the variance. In addition, we compared the RSA magnitude and maxima location for these methods.

### *Statistical Analysis*

Statistical tests are identified in the text where appropriate. Unless otherwise noted, the RSA pattern is reported as means ± SE and statistical values as means ± SD. Significance calculations were made with the Wilcoxon signed-rank test because the data set was too small for an assumption of normal distribution to be made ($n = 10$). Test results were considered significant at $P < 0.05$.

## RESULTS

### *Group 1*

The RSA pattern (Avg80) of *subject YN1* in supine and standing sessions is presented in Fig. 2 with the error estimation, showing differences in magnitude and phase between postures. The RSA patterns (Avg80) of *subjects YN2–YN10* also show differences between postures (presented in Fig. 3 without the error estimation, to avoid dense display); the typical error is similar to that of *subject YN1*.

As expected, instantaneous HR increased during inspiration and decreased during expiration. Table 1 summarizes statistical measurements derived for the Avg80 estimator with their significance level. The RSA magnitude $P_{Avg80}$ in standing posture was significantly lower than in supine posture, by an average of 52%. The average error over the RSA pattern $SE_{Avg80}$ (as presented in Fig. 2) was 45% lower in supine compared with standing posture because of the shorter standing session. The phase of the RSA pattern maxima $\phi^{max}_{Avg80}$ in standing posture was significantly shifted to the right by 11.4% of the respiration period compared with supine posture. Expiration duration was calculated in two different ways. First, the difference between the RSA pattern maxima and minima gave a change from 49% to 55% of the respiration period for supine and standing postures, respectively. Second, the difference between the RSA pattern maxima and expiration onset trigger gave a change from 47% to 58% of the respiration period for supine and standing postures, respectively.

In addition, the variances between the Avg80 estimator for the RSA pattern and the two other estimators (Avg100 and Med100) are given in Table 1. This is given for the difference between the entire waveforms, the difference in magnitude, and the differences in the maxima locations.

### *Group 2*

The results are presented here for the seven subjects with higher respiratory signal quality. The RSA patterns (Avg80) of *subject TN2* from *sessions A*, *B*, and *C* are presented in detail in Fig. 4 with standard error estimation. For subjects *TN3*, *-4*, *-6*, *-8*, *-11*, and *-12*, the RSA patterns (Avg80) are presented in Fig. 5 without error estimation (standard errors are similar to those for *subject TN2*). The RSA magnitude and pattern remain approximately the same for *sessions A*, *B*, and *C*. This may suggest a long-term consistency of the RSA pattern as a nonscalar index of vagal activity. Only one of the seven subjects in the selected group showed a variable RSA pattern over time. In the remaining eight subjects (*TN1*, *-5*, *-7*, *-9*, *-10*, *-13*, *-14*, and *-15*) with the lower respiration signal quality, five also showed a clear, consistent pattern (not shown). Table 2 summarizes statistical measurements derived from this data set, taking into account the subgroup of seven subjects with higher respiration signal quality. There was no significant difference between the three sessions in any of the above statistical properties. This result agrees with the long-term RSA pattern consistency effect. Grouped mean maxima location for the three sessions was $\overline{\phi^{max}_{Avg80}} = 3.29 \pm 0.47$ rad. In addition, values are given for the variances between Avg80 and the two other estimators (Avg100 and Med100) for the difference between the entire waveforms, the difference in magnitude, and the differences in the maxima locations.

## DISCUSSION

We have used two groups of healthy subjects to lay the baseline of RSA patterns and to underlay their features: response to standing, stability in successive recordings, and individuality of the shape of the RSA patterns. In *group 1*, we obtained a significant 52% decrease in magnitude and 11.4% right-shift phase lag when we compared supine and standing postures. The decrease in magnitude is in agreement with the literature, showing that our method is consistent with other methods for quantifying RSA magnitude (22). The phase difference may partly be ascribed to mechanical differences between supine and standing breathing patterns, resulting in

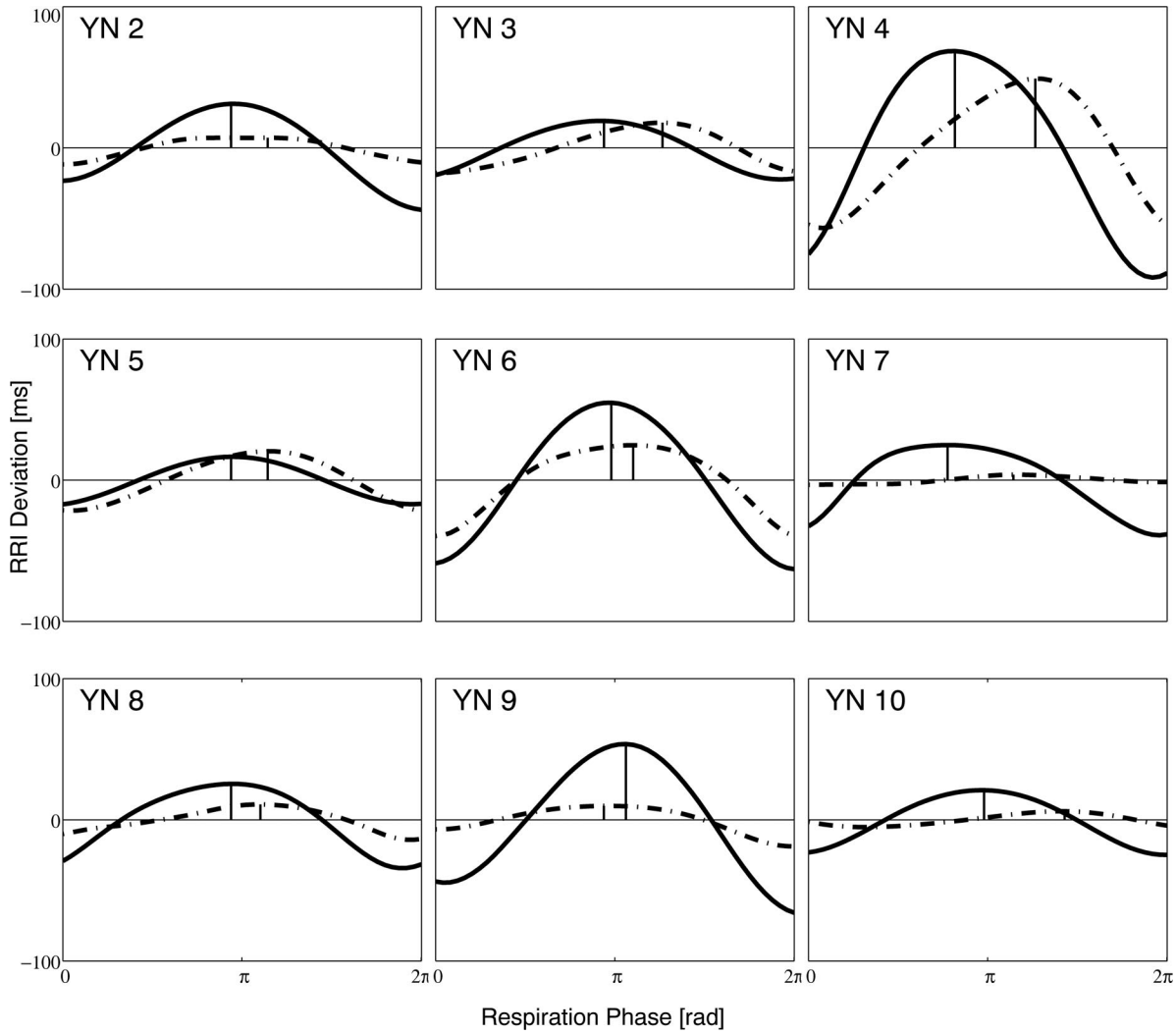


Fig. 3. RSA pattern of normal *subjects YN2–YN10* (*group 1*) at supine rest (solid lines) and standing posture (dash-dot lines). Magnitude and phase differences are clearly seen (vertical lines). Origin is the onset of expiration.

Table 1. *Group 1 statistical measurements*

| Posture | Supine | Standing | Units | *P* Value |
|---|---|---|---|---|
| HR | 63±6 | 77±8 | beats/min | <0.006 |
| Respiration rate | 16.9±3.3 | 17.1±1.7 | breaths/min | |
| $P_{Avg80}$ | 81±41 | 39±30 | ms | <0.006 |
| $SE_{Avg80}$ | 4.7±3.2 | 8.6±3.4 | ms | <0.004 |
| $\phi^{max}_{Avg80}$ | 2.9±0.3 | 3.7±0.5 | rad | <0.004 |
| $\phi^{min}_{Avg80}$ * | 6.1±0.3 | 0.2±0.4 | rad | <0.004 |
| Expiration duration† | 3.1±0.4 (49%) | 3.5±0.6 (55%) | rad | <0.06 |
| Expiration duration‡ | 3.0±0.3 (47%) | 3.6±0.5 (58%) | rad | <0.04 |
| Var (Avg80 − Avg100) | 7.7±5.7 | 16.5±14.4 | % | |
| Var (Avg80 − Med100) | 4.5±2.3 | 21.0±21.9 | % | |
| Var ($P_{Avg80}$ − $P_{Avg100}$) | 6.1±1.9 | 18.9±6.0 | % | |
| Var ($P_{Avg80}$ − $P_{Med100}$) | 3.2±1.0 | 15.8±4.0 | % | |
| Var ($\phi^{max}_{Avg80}$ − $\phi^{max}_{Avg100}$) | 6.8±2.2 | 10.4±3.3 | % | |
| Var ($\phi^{max}_{Avg80}$ − $\phi^{max}_{Med100}$) | 4.6±1.5 | 13.9±4.4 | % | |

Values are means ± SD. HR, heart rate; Avg80, method averaging 80% of respiratory cycles (present study); Avg100, method averaging 100% of respiratory cycles; Med100, method using median R-R interval value for 100% of respiratory cycles; $P_{Arg80}$, peak-to-peak magnitude of final respiratory sinus arrhythmia (RSA) pattern; SE, standard error; ϕ, phase; Var, variance; $\phi^{max}$, phase of maximal value. *Values are modulus 2π; the 2 values are 0.4 rad apart. †Calculated with RSA pattern minima and maxima. ‡Calculated with RSA pattern maxima and expiration onset trigger.

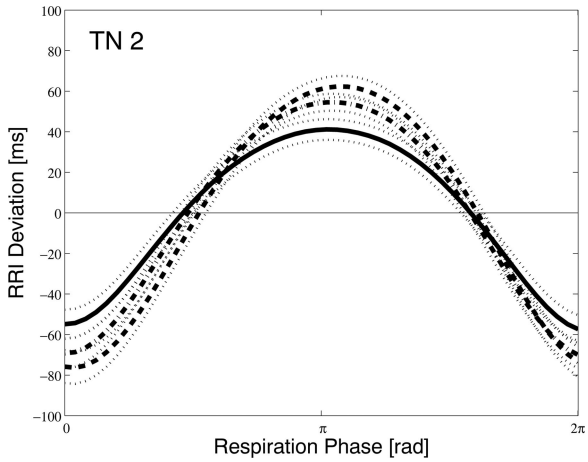


Fig. 4. RSA pattern of *subject TN2* (*group 2*) in the 3 sessions [*A* (dash-dot line), *B* (dashed line), and *C* (solid line)]. Error estimation is marked for each trace (dotted lines). Note the long-term consistency of the RSA pattern over the various sessions.

Table 2. *Group 2 statistical measurements*

| | Days | | | |
|---|---|---|---|---|
| | *A* | *B* | *C* | Units |
| HR | 68.1±5.2 | 71.0±8.3 | 69.1±6.2 | beats/min |
| Respiration rate | 14.9±1.5 | 15.1±1.3 | 14.1±1.0 | breaths/min |
| $P_{Avg80}$* | 78±30 | 62±39 | 72±33 | ms |
| $SE_{Avg80}$ | 5.1±2.3 | 4.0±1.1 | 4.8±2.3 | ms |
| Var (Avg80 − Avg100) | 7.6±2.4 | 8.2±3.7 | 6.5±3.8 | % |
| Var (Avg80 − Med100) | 8.7±4.1 | 6.7±2.3 | 7.5±3.4 | % |
| Var ($P_{Avg80}$ − $P_{Avg100}$) | 8.7±3.3 | 8.0±3.0 | 9.5±3.6 | % |
| Var ($P_{Avg80}$ − $P_{Med100}$) | 5.6±2.1 | 6.0±2.3 | 7.3±2.7 | % |
| Var ($\phi^{max}_{Avg80}$ − $\phi^{max}_{Avg100}$) | 3.5±1.3 | 2.5±1.0 | 4.2±1.6 | % |
| Var ($\phi^{max}_{Avg80}$ − $\phi^{max}_{Med100}$) | 3.7±1.4 | 2.5±0.9 | 5.4±2.1 | % |

Values are means ± SD. *Calculated peak to peak.

different chest diameter change patterns as measured by the Respitrace pneumoplethysmograph instrument. In addition, a 6–9% increase in the expiration period (increased expiration -to-inspiration ratio) is obtained by applying the two expiration duration calculation methods and was ascribed to the mechanics of respiration. Expiration is characterized by air flowing out from the lung spontaneously without any muscular activity involved (as opposed to inspiration). In the standing position, the diaphragm must move upward spontaneously against the simple gravitational force pulling the viscera downward (compared with supine position); the expiration will then take longer, increasing the expiration-to-inspiration ratio. Another cause of horizontal-standing phase differences may be an alteration in baroreflex phase shift at the respiratory frequency (see, e.g., Fig. 14 in Ref. 8), possibly because of different contributions of the vagal and the sympathetic arms of the baroreflex to the heart. The respiration rate and tidal volume are also important factors controlling RSA magnitude, phase, and possibly the overall RSA pattern. Although the respiration rate was similar between postures (Table 1), the tidal volume was not measured. The effect of these factors should be addressed in future studies.

In *group 2*, we may have found the first evidence for long-term consistency (and individuality) of RSA pattern obtained from sessions in the same subject several weeks apart (6 of 7 subjects with high and 5 of 8 with low respiratory signal quality). This consistency effect should be investigated further for a longer time between sessions to validate possible applications for RSA pattern as a new nonscalar index of vagal activity. Consistent individual features over 1 yr were observed in the past with circulatory power spectra (13). Consistency

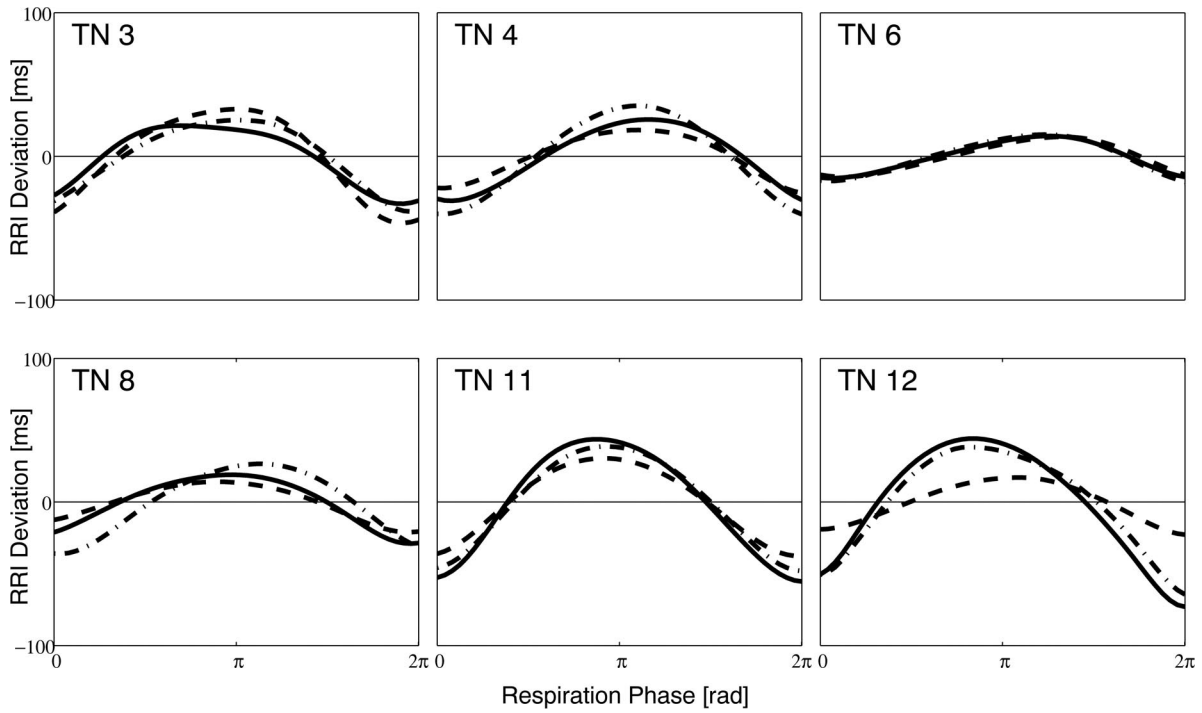


Fig. 5. RSA pattern of subjects *TN3*, *-4*, *-6*, *-8*, *-11*, and *-12* (*group 2*) in 3 sessions [*A* (dash-dot lines), *B* (dashed lines), and *C* (solid lines)] Note the long-term consistency of the RSA pattern over the various sessions for each subject (excluding *TN12*). Also note the variations among subjects.

could be used as a research tool for long-term changes of a subject's RSA pattern behavior, such as the response to drug treatment, recovery from disease, or autonomic changes due to exercise. An important diagnostic application would be detection of changes in RSA pattern related to a change in clinical condition of the subject.

We have also observed a possible individuality of RSA pattern characterization, which give rises to a possible "fingerprint" effect. This may lead to some interesting research applications such as trying to correlate the subject's specific RSA pattern with other autonomic functional characteristics, to achieve better understanding of autonomous control. A larger study group is unlikely to show unique RSA patterns. Instead, we expect to obtain various RSA pattern types shared among subjects. This may allow quantitative characterization of different autonomic function modes.

When we compare the location of the maxima of the RSA pattern in the supine session of *group 1* (2.9 ± 0.3 rad, pneumoplethysmograph method) and *group 2* (3.3 ± 0.5 rad, impedance method), we obtain a difference of 0.4 rad (6.7%). This is ascribed to differing recording instrumentation. The absolute phase of the RSA pattern is dependent on the recording method of the respiratory signal and may cause variations in the order of 0.5 rad. Hence, physiological interpretation of the absolute phase should be considered with caution. Comparing our RSA pattern estimator (Avg80) with two previously published methods (Avg100 and Med100), we consider the differences in RSA pattern, RSA magnitude, and maxima location.

### *Difference in RSA Pattern*

Average variance in *group 1* was 7.7% and 16.5% for supine and standing, respectively (Avg80 − Avg100) and 4.5% and 21.0% for supine and standing, respectively (Avg80 − Med100). Average variance in *group 2* (supine) was 7.4% (Avg80 − Avg100) and 7.6% (Avg80 − Med100). These differences (for both groups) of 5–8% for long (30–60 min) supine recordings and 17–21% for short (5 min) standing recordings are significant enough to distort the waveform of the RSA pattern when long-term consistency and differences between subjects are considered. In the Avg100 case, the distortions are related to outliers included in the averaging. In the Med100 case, the distortions are related to the independent decision for the median at each respiration phase. As a result, the median value at each phase is taken from a different respiration cycle, reducing the smoothness of the final Med100 waveform. These effects will be more pronounced in short recordings and are expected to increase further in recordings contaminated with arrhythmia, where filtering the outliers is more crucial.

### *Difference in RSA Magnitude*

Variance in *group 1* was 6.1% and 18.9% for supine and standing, respectively (Avg80 − Avg100), and 3.2% and 15.8% for supine and standing, respectively (Avg80 − Med100). Average variance in *group 2* (supine) was 8.7% (Avg80 − Avg100) and 6.3% (Avg80 − Med100). When considering the use of this method as a measure for RSA magnitude, the 3–9% variance in the long supine recording is acceptable, whereas the 16–19% variance in the short standing recording may be regarded as too high. This emphasizes the importance of our outlier rejection technique when estimating RSA magnitude from short recordings.

### *Difference in Maxima Location*

Variance in *group 1* was 6.8% and 10.4% for supine and standing, respectively (Avg80 − Avg100), and 4.6% and 13.9% for supine and standing, respectively (Avg80 − Med100). Average variance in *group 2* (supine) was 3.4% (Avg80 − Avg100) and 3.9% (Avg80 − Med100). The variance of 3–7% for the long supine recording and the variance of 10–14% for the short standing recording can be regarded as unacceptable for studies aimed to examine the phase. This is based on the average phase differences of 0.8 rad (12.7%) observed in *group 1*, where even additional 3% distortion may bias the results by 27% (3.4/12.7 = 0.27).

In most of the cases described above, the variance of the comparison between Avg80 and Med100 was lower than the variance of the comparison between Avg80 and Avg100, suggesting that the use of the median value is better than averaging all the respiration cycles. However, the Med100 had its own drawback of treating each respiration phase independently when additional information is embedded in the way each waveform is changing throughout the respiration cycle. This additional information is exploited in our outlier rejection procedure, taking the integral differences between entire cycles.

Several drawbacks of the suggested method must be considered. First, at least 5 min of stationary recording is required for reasonable error. Dinh et al.(7) suggested breath-by-breath short time analysis of the RSA pattern. However, according to our results, a single-breath RSA pattern has a very low resolution limitation that may obscure valuable information. Second, 20% of the respiratory cycles that may contain important information are regarded as outliers during our averaging process. Finally, the method requires simultaneous recording of ECG and respiration. This may limit future clinical applications.

Further work by our group includes the analysis of residual RSA patterns in humans after heart transplant. Preliminary results from the heart transplant data show sufficient accuracy and robustness of the method for describing the RSA pattern, which is one order of magnitude smaller in amplitude and often contaminated with arrhythmia. The RSA pattern may assist in the investigation of recovery processes and mechanical modulation in heart transplant patients.

In conclusion, the time-domain RSA pattern characterization is complementary to the frequency-domain and statistical methods. We presented a refinement for the estimation procedure and presented the baseline of several normal conditions. This method may provide exciting insight into the effects of vagal activity during normal and altered sympathetic and vagal conditions as well as into changes in clinical conditions in specific cardiac or respiratory diseases (yet to be explored).

## ACKNOWLEDGMENTS

The authors thank Y. Goren for assisting with the collection of the data set for *group 1*.

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