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Comparison of Different Algorithms for Evaluation of Respiratory Sinus Arrhytmia: Cross-Correlation Function Histogram Analysis and Regression Analysis

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Summary

Three algorithms for assessment of respiratory sinus arrhythmia (RSA) have been evaluated: cross-correlation function, histogram analysis and regression plot. The algorithms were tested experimentally in a group of 11 subjects. A cross-correlation function with a high time resolution (1 ms) was used for investigation of the time lag between instantaneous heart rate and respiration (CTL). This time lag was not affected by the breathing rate in a range of 8 to 29 breaths per minute. A mathematical model of CTL compared with experimental results indicates that respiratory sinus arrhythmia is probably modulated directly by the respiratory network in the brainstem rather than by a baroreflex in the range of breathing rate investigated. Histogram analysis reflects the impact of inspiration and expiration on respiratory sinus arrhythmia. For this purpose heart rate changes were separated into two distributions (inspiration – expiration). The result value (U-VAL) of the Mann-Whitney U-test reflects the impact of respiration on heart rate variability. Regression analysis of heart rate versus respiration shows that the heart rate increase is more closely coupled to inspiration than the heart rate decrease to expiration. Both, CTL and U-VAL are thought to be useful parameters for clinical investigation of RSA.

Key words

Respiratory sinus arrhythmia – Cross-correlation function – Histogram analysis – Computer

Introduction

It is well known that beat to beat variation of the heart rate is modulated by respiration. The heart rate tends to increase during inspiration and decrease during expiration. This phenomenon is called respiratory sinus arrhythmia (RSA). In 1871, Hering concluded that the heart rate response to respiration was caused by a reflex of pulmonary origin. He suggested pressure- sensitive lung receptors as the afferent and the vagus nerve as the efferent pathway of the reflex (Grossman *et al.* 1990). Later, Clynes (1960) found a biphasic response to respiration. Expiration has much smaller effect on the heart rate than inspiration (Angelone and Coulter 1964, Brecher *et al.* 1955).

According to our present knowledge the influence of respiration on the cardiac rhythm may mainly originate from two sources under physiological conditions:

(1) It may be due to respiration-induced changes in arterial blood pressure that influences cardiac frequency *via* baroreceptors, as established by Matthes and Ebeling (1948).

(2) It may be originate in rhythm generators in the CNS as suggested by Heymans (1992).

Previous studies showed more specifically that RSA is correlated to tidal volume (Davies and Neilson 1967, Grossman *et al.* 1990, Hirsch and Bishop 1981) as well as to respiratory frequency: the amplitude of RSA has its maximum at a respiratory frequency of 6 breath/min (Angelone and Coulter 1964, Davies and Neilson 1967).

Some results of this study were presented at the "Fourth International Symposium on the Autonomic Nervous System" of the American Autonomic Society (October 1993, Nashville, Tennessee, USA)

A frequently used technique to describe heart rate variability is the fast Fourier transformation, introduced by Kitney and Rompelmann (1980). However, correlation analysis of heart rate and respiration may also be useful since this method directly reflects the breathing effects on the heart rate and possible deviations under pathological conditions.

Bernardi *et al.* (1992) were first to establish cross spectra correlation between heart rate and respiration, yet with a poor time resolution. Since the heart rate is obtained as a discontinuous function of time while respiration is measured as a continuous function, information about interbeat changes of respiration may be lost when using Fourier analysis techniques (Bernardi *et al.* 1992).

In this study, three mathematical methods for investigation of respiration and its effect on heart rate variability are employed.

(1) A cross-correlation function based on regression analysis is implemented to investigate the time shift between respiratory sinus arrhythmia and respiration with a high time resolution of 1 ms.

(2) The correlation diagram is used to extract information on the relation between heart rate and respiration.

(3) Two distributions of heart rate are obtained from histogram analysis, one for inspiration and the other for expiration.

The information gained by these methods may throw light on the origin of respiratory sinus arrhythmia: is there a central pacemaker for both – respiration and heart rate – or is it respiration which causes changes in heart rate *via* a reflex arc ?

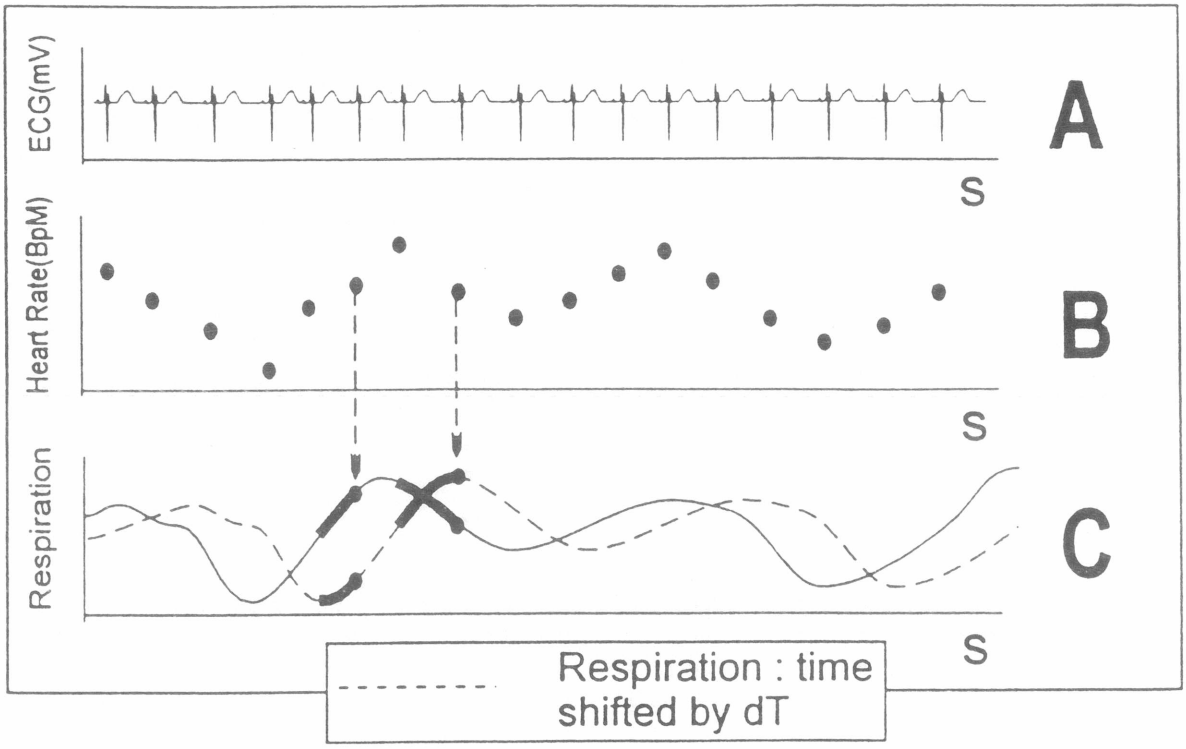

Fig. 1
The reciprocal relationship of the time interval between successive R waves in the ECG (A) represents the instantaneous heart rate (B). Since heart rate is discontinuous, it can only be measured at certain times, i.e. at the occurrence of R waves. The mean value of the continuous breathing signal in the R(n)-R(n+1) interval is compared to heart rate at the corresponding times of R(n+1)-wave.

Methods

Subjects and recording technique

Eleven male subjects (26–34 years) without history of cardiopulmonary disease were included. All subjects gave their informed consent and the study was approved by the local ethics committee.

The subjects were connected to an ECG monitor (Hellige, SMS 181, low-cut frequency: 55 Hz, amplification: 1000) by three electrodes in an Einthoven II configuration. A mercury filled chest belt

was used to record respiratory movements. The chest-belt movement correlates very well with tidal volume (Grossman *et al.* 1990). ECG and chest-belt signals were sampled at a frequency of 1 kHz and digitized. Digitization was carried out using an analog-to-digital converter with a microprocessor and RAM, including software tools used for signal preprocessing (Microstar Laboratories, DAP 800/3, 12 bit resolution, Avenue n. e. Bellevue, Scottsdale, USA). The digital signal was transferred into a 386 AT computer (SIKOS, Stein, Germany), fitted with a math coprocessor (ULSI, Tokyo, Japan).

All subjects were asked to sit and rest for 5 min before the recordings started. During a recording period of 2 min, subjects were told to breath regularly, at their spontaneous constant frequency and tidal volume. After a resting interval of 1 hour, subjects were asked to breath at a high frequency.

The ECG signal recorded during the two recording periods was processed in order to obtain R-R intervals with precision of 1 msec. Thereafter, the reciprocal of the R-R interval was computed to get the instantaneous heart rate in the time domain. Finally, the respiration signal was filtered with a sliding average low-pass filter and compressed for data reduction. The mathematical methods used here to investigate heart rate variability and respiration were implemented using the Turbo-Pascal computer language.

The software supports the evaluation of all classical parameters used for the assessment of heart rate variability, i. e. mean heart rate, the mean R-R interval, standard deviation of the R-R interval, root mean square of successive differences (RMSSD), (Ewing *et al.* 1985), range of respiratory sinus arrhythmia (Angelone and Coulter 1964), fast Fourier spectrum of heart rate (Kitney and Rompelman 1980), minimum and maximum heart rate (Ewing *et al.* 1985).

As a useful addition to these parameters we calculated the respiratory frequency in respiration cycles per minute by using the autocorrelation function (Press *et al.* 1987). This parameter can be compared with respiratory frequency-dependent values such as range of respiratory sinus arrhythmia, RMSSD and standard deviation of R-R intervals.

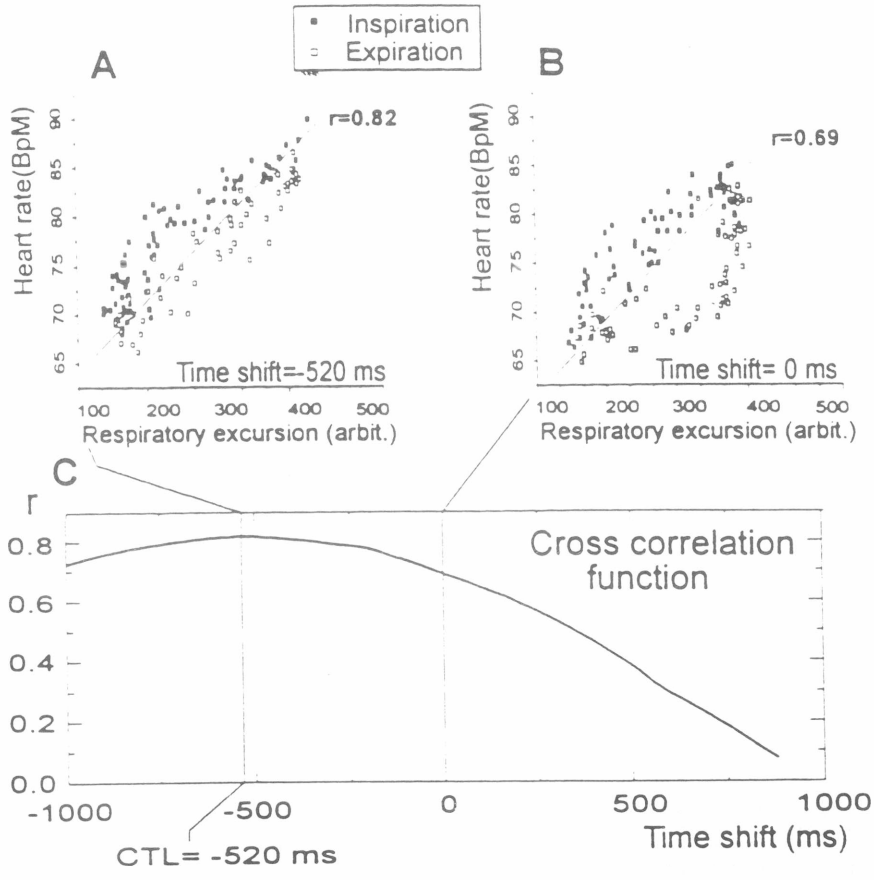

Fig. 2
Cross-correlation of the instantaneous heart rate and the thoracic excursion (specimen record, subject 8). The upper right diagram (B) shows plots of heart rate against thoracic excursions without any time shift, note the hysteresis loop. The upper left diagram (A) shows the same data with thoracic excursion shifted by −520 ms. The hysteresis loop disappears, the correlation coefficient becomes greater. The bottom diagram (C) shows the cross-correlation function. Each value on the curve represents the correlation coefficient with a time shift shown on the abscissa.

The cross-correlation function describes the time lags between two oscillatory signals. One of these two signals is delayed in time with a particular ΔT. In order to assess this delay, one signal is shifted at discrete steps until maximal correlation is achieved. This value describes maximal equality between both signals.

As the heart rate is a discontinuous and respiration excursions a continuous function, the continuous function has to be transformed into a discontinuous one (Fig. 1).

As the respiratory sinus arrhythmia is modulated by respiration, and the sine node could be seen as a pulse modulator which integrates vagal and sympathetic inputs from one heart beat to the next, it is necessary to compare each instantaneous heart rate with the average respiratory excursion in the whole R-R interval. This method is in accordance with the pulse modulator model of pacemaker activity introduced by Hyndman and Mohn (1973)

Shifting of the respiration signal is performed in 1 ms steps and the average value of the respiration signal in the respective R-R interval is used for correlation against the corresponding heart rate.

Plotting the average respiration signal against the respective heart rate leads to a scattergram shown in Figs 2A and 2B (specimen record). Correlation coefficients for each time shift between respiration and heart rate are depicted in Fig. 2C. At a particular time lag, the correlation coefficient reaches a maximum, i. e. best synchrony between heart rate and respiration. We will refer to this value as the cross-correlation time lag (CTL) between respiration and heart rate.

In addition, we calculated the cross-correlation function of heart rate and the first derivative of the respiration signal. This measure is assumed to reflect the influence of intrapulmonal pressure on systemic blood pressure. The resulting time shift between heart rate and the derivative of respiration is called CTL' (Fig. 2).

In order to investigate whether there is a relation between the amplitude of heart rate changes and changes of breathing movements, the regression plot was implemented using the scattergram of the velocity of the respiratory excursion and the difference between subsequent heart rate values.

The respiratory signal used for the scattergram was time shifted by CTL before plotting against heart rate changes in order to show the effect of breathing on the heart rate irrespective of the time lag.

Because of the possibly different effect of inspiration and expiration, correlation coefficients against the corresponding velocity of the respiratory excursion were calculated for the rising (R(inc)) and falling heart rate (R(dec)).

Heart rate variability is often described in a histogram. For evaluation of the differential impact of inspiration and expiration, it may be helpful to calculate two distributions of heart rate, one for inspiration and one for expiration. Quantitative differences between the histograms can be tested by the Mann-Whitney U-Test (Wilcoxon) for independent samples.

After shifting the respiration signal by CTL, heart rate changes are collected in two histograms, one for inspiration and one for expiration. The resulting U (Mann-Whitney-parameter) depends on the number of cases (Press *et al.* 1987). To become independent of the number of examined values, the resulting U was divided by the critical U(c) for $p = 0.05$. The resulting value (U-VAL) is independent of the number of examined values and can be used as a parameter of the respiratory effect on heart rate. Thus, U-VAL serves as a parameter for the conformity of the two distributions. Values greater than one indicate equal, values lower than one different distributions.

Theoretically, heart rate variability is composed of a mixture of respiration-dependent and respiration-independent variations. U-VAL in this context can be used to assess respiration-independent irregularities of the heart rate, since the respiration-dependent variance has been eliminated by the shifting procedure. U-VAL should not be considered as a statistical test of significance.

Results

Experimental results: Heart rate ranged from 54 to 105 beats per minute, mean respiration frequency was 12.83 ± 6.34 (mean $\pm$ S.D.) per minute) in all subjects with a range of 8 to 29. Spontaneous breathing rate was measured within the range of 8 to 15 breaths per minute with a mean of 10.24. High breathing rates had a mean of 17.73 with a range of 12 to 29 breaths per minute. The mean RMSSD was 49.29 ± 31.53 ms, the range of RSA 10.64 beats per minute.

Cross correlation: The mean CTL of all subjects was -44.75 ± 318 ms with a range of -720 ms to $+560$ ms. The positive time shifts indicate that the peak heart rate was reached before the end of inspiration, the negative values indicate that the heart rate was peaking after reversing to expiration. In contrast, mean CTL' was -1737 ± 535 ms with a range of -2820 to $+640$ ms.

Histogram analysis: The mean U-VAL was 0.28 with a standard deviation of 0.14. In all cases the U-VAL did not exceed 1, indicating a dependence of heart rate on respiration in all subjects.

Regression plot: The plots of heart rate changes were tested against velocity of respiratory excursion. The respiration movement was shifted by a time equivalent to the resulting CTL. Fig. 3 shows an example of subject 9 with a CTL of +80 ms. In this case, R(inc) was 0.76 and R(dec) 0.41.

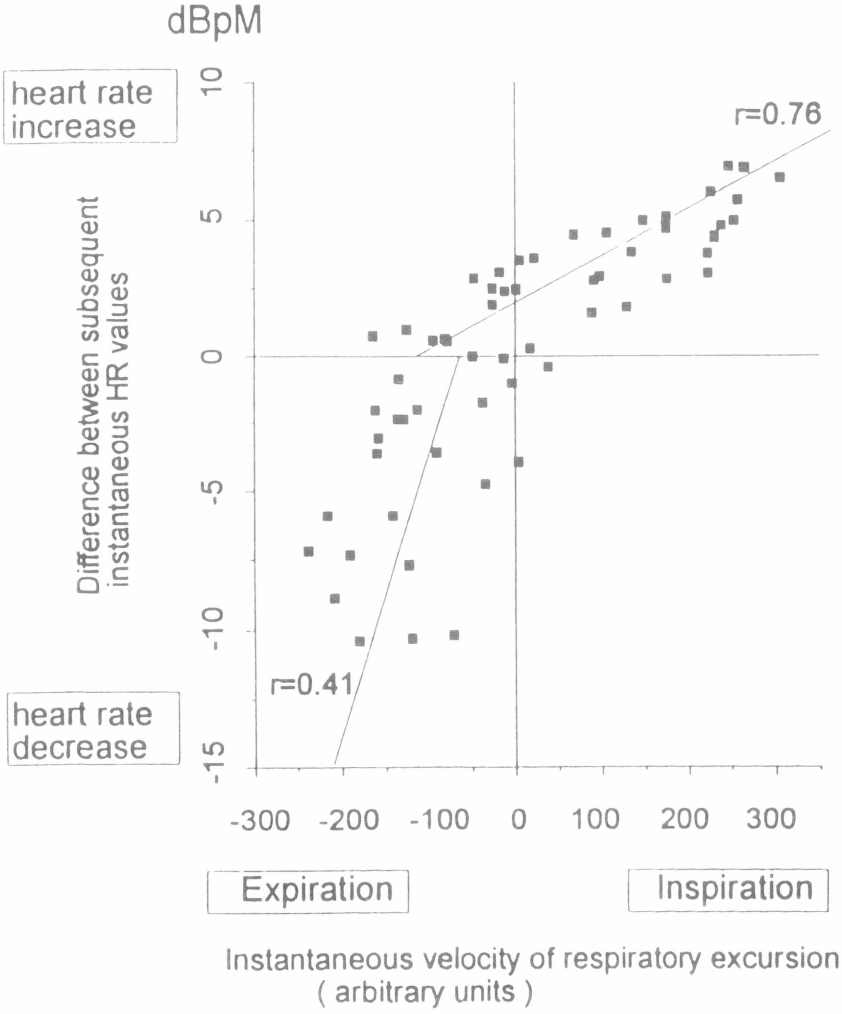

Fig. 3
Correlation diagram (subject 18) of heart changes rate against changes of thoracic perimeter. The regression line was calculated selectively for positive (R(dec) = 0.41) and negative (R(inc) = 0.76) heart rate changes due to respiration movement changes. The respiration signal was time-shifted with CTL = +80 ms. The upper part of this diagram represents rising heart rate values, the lower part falling heart rate. Inspiratory and expiratory movements are represented to the right and to the left of the central ordinate axis.

R(inc) was significantly higher than R(dec) in all subjects ($p<0.0001$) with a mean of 0.44 for R(inc) and 0.26 for R(dec).

With a matched pair Wilcoxon test the effect of normal breathing rate in contrast to the high breathing rate was tested for CTL, U-VAL and CTL'. Neither CTL nor U-VAL are affected by the breathing rate ($p>0.5$) and ($p>0.08$) respectively. U-VAL shows no significant changes with the breathing rate, although mean U-VAL for the normal breathing rate was 0.13 ± 0.02 and for high breathing rate 0.47 ± 0.32. On the other hand, CTL' shows a significant difference between normal and high breathing rates ($p<0.0001$).

In addition, we found that CTL' and breathing rate. CTL' of all subjects was significantly dependent on the breathing rate ($r = 0.85$, $p<0.01$).

Discussion

Angelone and Coulter (1964) found the influence of respiratory frequency on the heart rate variability to be maximal at a breathing rate of 6 breaths/min. Higher frequencies decreased RSA. In clinical practice RSA assessment was therefore concentrated on this frequency which is awkward for the patients because 6 breaths/min is far below the physiological breathing rhythm of about 14 breath/min. Unlike Angelone and Coulter (1964), we found no need for the choice of low breathing rates since at the frequencies investigated (8 to 29 breaths/min) neither U-VAL, reflecting the respiratory influence on the heart, nor CTL, reflecting the time lag between respiratory cycles and RSA, are dependent on the breathing rate. These parameters may therefore be obtained in clinical investigation at frequencies more convenient for the patient.

In contrast to Angelone and Coulter (1964), we could not find (in the frequency range studied) a frequency-dependent phase variation of respiratory excursion versus heart rate variability (Fig. 4). Rather the phase angle remained constant over the frequency range investigated by us.

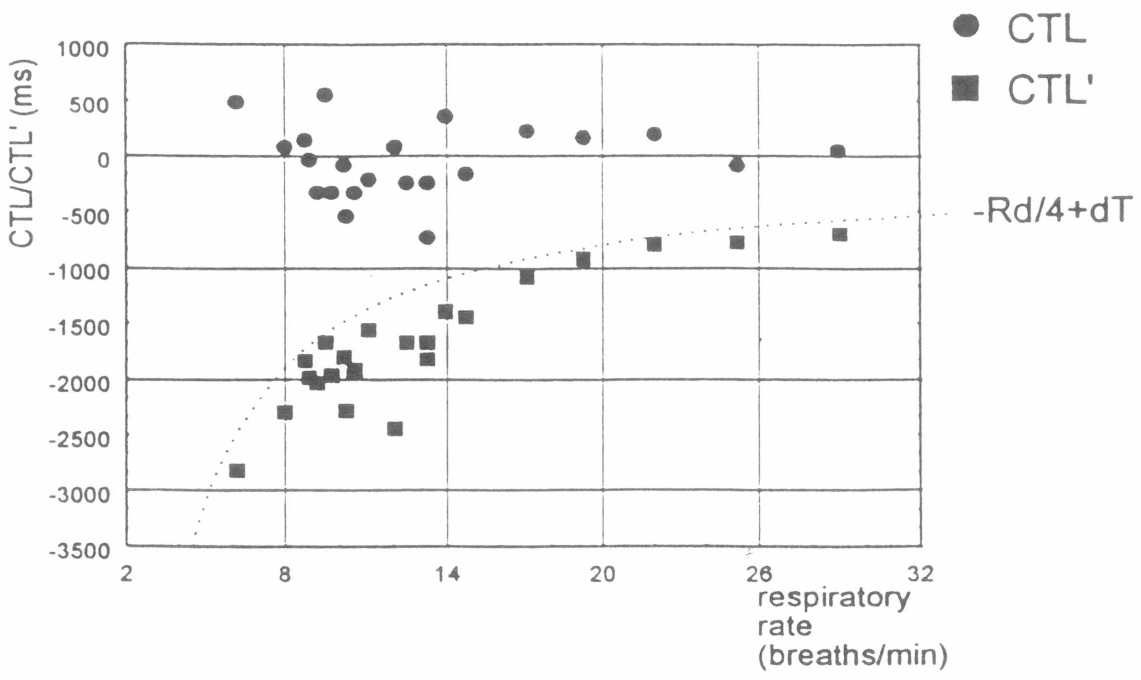

Fig. 4
CTL (circles) shows no dependence on respiratory frequency (RF), CTL' (squares) is positively correlated to RF with a good approximation to Rd/4, with Rd as the duration of one respiratory cycle (dotted line).

However, when calculating the time lag between the velocity of thoracic excursion and heart rate (CTL'), there is variability dependent on the breathing frequency. This finding is a consequence of the relationship between maximal velocity and maximal value of a sinusoidal signal. The former lags one quarter of the wavelength behind the latter.

Assuming a reflex origin of RSA, blood pressure changes, *via* baroreceptors, would be the adequate stimulus for heart rate modulation. A low intrapulmonal pressure during inspiration decreases systemic blood pressure and, as a consequence, induces an increase in heart rate (Brecher and Hubay 1955). The latency of this effect on RSA includes haemodynamic and neuronal mechanisms. The pressure in the lung varies with the negative phase of the first derivative of the thoracic excursion.

Therefore, if reflex mechanisms account for the covariation of respiratory and cardiac rhythms, CTL' should be the independent variable linked to the RSA irrespective of the respiratory frequency. CTL, in contrast, should depend on the respiratory frequency because of its delay by one quarter of the respiratory cycle. Therefore our results seem to indicate a common control of respiration and vagal tone, at least in normal, sitting subjects under resting conditions and in the range of breathing frequencies investigated.

A further argument is provided by the short time lag between the respiration cycle and respiratory sinus arrhythmia. The mean CTL (−44 ms) points to a common pacemaker of RSA and respiratory excursion since the delay of a reflex arc would be much in excess of −44 ms. Given the mean conductance velocity of 10 m/s for afferent A-δ-fibres and 15 m/s for efferent vagal unmyelinated and thin myelinated fibres, together with a distance of around 50 cm, the time shift would be more than −500 ms. This is true, even without taking into account synaptic delays and P-Q time.

The result of R(inc) and R(dec) indicates that the acceleration of heart rate is locked to inspiration. Expiration and the of slowing heart rate are less strongly coupled.

Since the inspiratory neuronal network in the brainstem has an inhibitory effect on the vagal nuclei *via* inhibitory interneurons, inspiratory activity probably has an impact on the vagus nerve (Spyer 1988). On the other hand, there is no experimental proof for connections between expiratory neurones and the autonomic nervous system.

The results presented here support the central nervous theory, i.e. a common generator for both respiratory sinus arrhythmia and respiration in the range of breathing rates greater than 8 breaths per minute. Work is in progress to investigate the interdependence at lower frequencies.

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