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Effect of respiratory rate on the relationships between RR interval and systolic blood pressure fluctuations: a frequency-dependent phenomenon

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Abstract

Objective: The aims of this study were to determine the relationships between oscillations in systolic blood pressure and heart period at different breathing frequencies and to investigate the role of sympathetic contribution to this relationship. **Methods:** Fourteen healthy volunteers underwent three randomized periods of controlled breathing at 6, 10 and 16 breaths/min. ECG (RR), respiratory signal (RESP) and systolic blood pressure (SBP) were continuously recorded. The component of RR and SBP oscillations related to respiration (RR_{Resp} and SBP_{Resp}) was defined by means of uni- and bivariate spectral analysis. The squared coherence (K^2) and phase between RR and RESP, and RR and SBP (RR-SBP) were also assessed. When the K^2 of RR-SBP in the respiratory band was > 0.5, we considered the phase and calculated the closed-loop gain between the two signals. Seven subjects were also studied after chronic metoprolol treatment. **Results:** Although the mean values of RR and SBP did not differ between the three periods of breathing, the higher the respiratory rate, the smaller the RR_{Resp} and SBP_{Resp}. The phase was always negative (SBP_{Resp} changes preceded RR_{Resp} changes), thus suggesting a baroreflex link. The higher the respiratory rate, the lower the gain and phase. Pharmacological β-adrenoceptor blockade increased the gain and shifted the phase, but the relationships found at baseline between the respiratory rate and both the gain and phase remained unchanged. **Conclusions:** The effect of breath rate on the relationship between heart rate and systolic pressure variabilities is a frequency-dependent phenomenon that is also independent of the sympathetic drive.

Keywords: Heart rate variability; Respiratory sinus arrhythmia; Systolic blood pressure variability; Metoprolol; Baroreflex gain; Cardiorespiratory index; Bode plot

1. Introduction

It was in 1733 that Stephen Hales first described the fact that respiratory activity is capable of modifying heart rate and blood pressure oscillations in the horse. Since then, a large number of studies have analysed the effects of breathing on cyclic heart rate changes in man, a phenomenon known as respiratory sinus arrhythmia (RSA).

Spectral analysis of heart rate offers a good [1,2] and reproducible [3] estimate of RSA. Moreover, when heart rate and systolic blood pressure variabilities are simultaneously processed by means of bivariate spectral analysis, it is possible to obtain a reliable analysis of the inter-relationships between the two signals [4]. Baroreflex sensitivity in man can be investigated both invasively and non-invasively, and spontaneous assessment by means of the spectral analysis of the variability in the RR interval and SBP signals has recently been proposed. Some authors have calculated the modulus of cross-spectrum of respiratory rate–systolic blood pressure (RR–SBP) for frequencies ranging from 0.07 to 0.129 [5] or 0.14 Hz [6], whereas others have used the square root of the ratio of the RR and SBP variabilities in the low- and/or high-frequency band [7,8]; an average index based on both low and high frequency oscillatory components has also been suggested [9].

It is already known that increases in the breathing rate are associated with a reduction in both RSA [10–15] and

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systolic blood pressure oscillations [8,10,11]; however, there are few data relating to the effects of different breathing rates on the relationship between RR and SBP variabilities [17,18]. In particular, it is not known whether the respiratory rate is capable of influencing baroreflex gain as assessed by means of spectral analysis. At rest while in the supine position, respiration is associated with parallel changes in vagal and sympathetic activities on the sino-atrial node: at a rate of more than 9 breaths/min (0.15 Hz), heart rate fluctuations are primarily mediated by vagal modulation; at lower frequencies, RSA is dominated by both vagal and sympathetic modulation [14,18]. Sympathetic activity is responsible for blood pressure variability at 0.1 Hz (Mayer waves). The differences in the inter-relationships between respiration and cardiovascular variables in the low- (below 0.15 Hz) and high-frequency (above 0.15 Hz) bands obtained by spectral analysis may be due to the different contribution of sympathetic activity in these two bands.

The aim of this study was to determine whether different breathing rates modify the relationship between heart rate and systolic blood pressure oscillations in normal subjects and to explore the contribution of sympathetic drive to this relationship. Part of this work has been reported elsewhere [19].

2. Methods

2.1. Subjects

We studied 14 healthy volunteers, nine males and five females, aged 27 ± 3 years (mean $\pm$ s.d.). None were on medication, all were non-smokers, and all engaged in average levels of physical activity. All of the subjects gave their informed consent, and the study was approved by the local Ethics Committee. Seven subjects were also studied after chronic β-adrenoceptor blockade with slow-release metoprolol (200 mg orally once daily for 10 days).

2.2. Experimental protocol

The experiments were performed in the morning in a quiet and light-attenuated room, whose ambient temperature was kept at around 24°C. The subjects were asked to remain at rest in a supine position for 10 min, and then to control their respiratory rate with the help of a metronome at different breathing rates: 6 (near 0.10 Hz), 10 (near 0.16 Hz) and 16 (near 0.27 Hz) breaths/min. The sequence of the breathing rates was randomized, with each paced breathing period lasting for 5 min. The three periods were separated from each other by an interval of 5 min during which the subjects were allowed to breathe spontaneously. Tidal volume was not controlled, in order to avoid alveolar hypo- or hyperventilation [17,20].

2.3. Data collection and analysis

2.3.1. Signal acquisition

During each session, the following signals were continuously recorded: ECG by means of a conventional bedside monitor (Hewlett Packard model 78354C), the respiratory signal by means of an impedance pneumograph (Hewlett Packard model 78354C), and blood pressure by means of a photoplethysmographic finger transducer (Finapres model 2300, Ohmeda). The self-adjustment mechanism of the Finapres was turned off during the paced breathing period, although it was engaged between the three sessions. The data were stored on a personal computer with signal conditioning, an anti-aliasing low-pass filter and a 12-bit A/D interface.

The ECG signal was acquired at a sampling rate of 1 kHz, and the other signals at a sampling rate of 250 Hz. A real-time program [21] detected the ECG R-wave signal and measured the beat-to-beat intervals and beat-to-beat systolic pressure. When present, artifacts were removed and corrected by means of linear interpolation with the previous and following beats. From the visual inspection time series of the tachogram, systogram and respirogram, periods of 256 beats were selected and considered eligible for subsequent analysis.

2.3.2. Time domain analysis

For each step of the protocol, the mean values of the RR intervals (ms), the peak–valley RR intervals (the longest minus the shortest RR interval; ΔRR), and systolic and diastolic blood pressure (mmHg) were calculated.

2.3.3. Spectral analysis

Frequency domain variability was analysed using an autoregressive method on the RR intervals, systolic blood pressure (SBP) and the respiratory signals (RESP) (Fig. 1). The model order was selected using the Akaike Information Criterion [22]. The total power (range 0 to 0.4 Hz) of the RR intervals (TP–RR) and SBP intervals (TP–SBP) was calculated and expressed in ms^2 and $mmHg^2$, respectively. Spectral components were obtained by means of a decomposition method in order to measure the power and centered frequency of each peak. The respiration-related component in the RR interval (i.e. RSA; RR_{Resp}; ms^2) and SBP (SBP_{Resp}; $mmHg^2$) spectra were identified by means of cross-spectral analysis (see below).

2.3.4. Cross-spectral analysis

The squared coherence (K^2) and phase (Φ) between the RR intervals and RESP (RR–RESP), and between the RR intervals and SBP (RR–SBP), were assessed by means of bivariate spectral analysis [23] (Fig. 2). Coherence evaluates the degree of correlation between the powers of two signals in the frequency band, and Φ quantifies the delay or lag between the signals. When K^2 exceeds 0.5

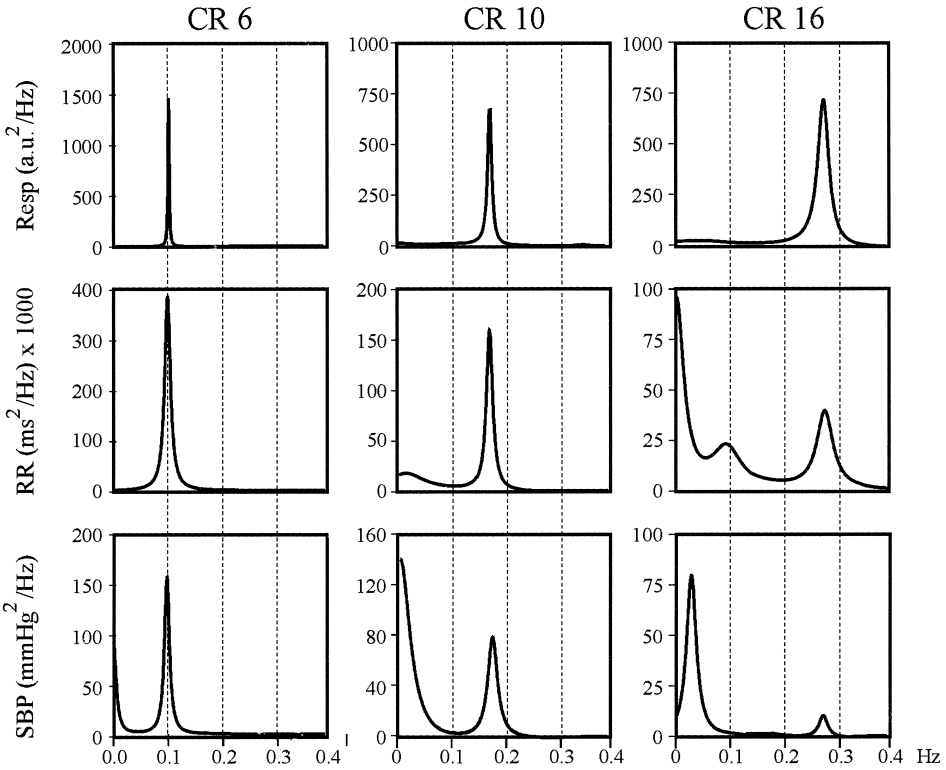

Fig. 1. Autoregressive power spectra of respiratory signal (RESP), tachogram (RR) and systogram (SBP) during controlled respiration at 6 (CR 6), 10 (CR 10) and 16 (CR 16) breaths/min in one subject. During the three paced breathing periods, the oscillations in the RR and SBP spectra are clearly synchronous with the respiratory peak. a.u., arbitrary units.

(range 0 to 1) at any frequency, the phase function (value between $-180°$ and $+180°$) provides a reliable assessment of the time relationships between the two signals. Although in the closed-loop model we used, the simple phase value makes it difficult to identify which signal leads and which follows, we considered the first signal as

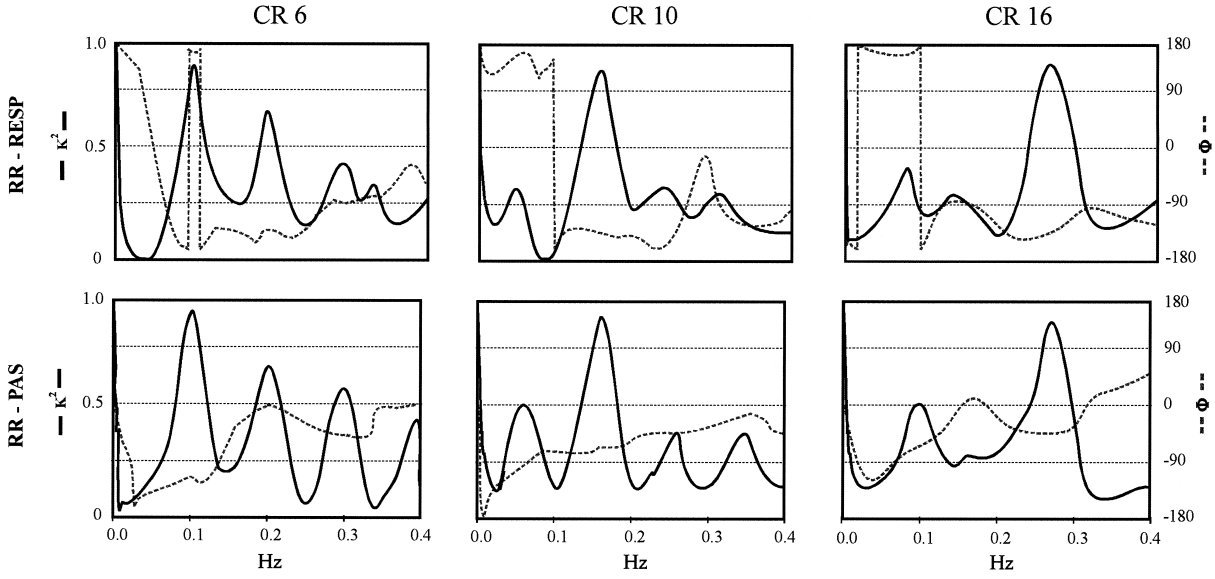

Fig. 2. Examples of cross-spectral analysis between the RR interval and breathing signal variabilities (RR–RESP; top panels), and between the RR and systolic pressure variabilities (RR–SBP; bottom panels) at three controlled respiration rates (CR) in one subject. Note the high value (>0.75) of the squared coherence (K^2; solid line) in the respiratory band between the two signals. The phase (Φ; dotted line) in the respiratory band of the RR–SBP cross-spectra changes at different frequencies of breathing: the higher the respiratory rate, the smaller the value of the phase.

following the second when the Φ value between two signals was $< 0°$; on the other hand, a Φ value of $> 0°$ suggests that the first signal precedes the second.

When K^2 at the respiratory frequency in the cross-spectrum between RR_{Resp} and SBP_{Resp} was > 0.5, we considered the Φ value and calculated the gain (α index) as the square root of the ratio of the RR and SBP variabilities (ms/mmHg) [7]: Φ was expressed in both degrees and seconds [7,14]. The gain was also analysed by means of Novak's cardiorespiratory index (CRI; ms/mmHg): $CRI = [(RR_{Resp}/RRmean)/(SBP_{Resp}/SBPmean)]^{1/2}$ [17]; and the gain–frequency responses (Bode plot) as 20 log (output/input): input was SBP_{Resp}, and output was RR_{Resp}, expressed in units of decibels (db).

2.4. Statistical analysis

The results are given as means ± s.d. The total power of RR and SBP, as well as the powers of RR_{Resp} and SBP_{Resp}, were transformed into their natural logarithms because their distributions were strongly skewed towards large values. After log transformation, all of the data had a normal distribution. One-way ANOVA for repeated measures was performed in order to evaluate the differences between the three phases of the study. Two-way ANOVA for repeated measures was performed in order to evaluate the effects of metoprolol on the relationship between the breath rate and the examined variables. The Student-Newman-Keuls test was used to evaluate post hoc differences. A P-value < 0.05 was considered significant.

3. Results

3.1. Baseline

During the three metronome-paced breathing periods, the mean values of RR, SBP and DBP did not differ (Table 1).

ΔRR showed a progressive reduction at increasing breathing rates, which was significant only when the results obtained at a breathing rate of 16 breaths/min were compared with those obtained at a rate of 6 breaths/min (Table 1).

The mean value of TP–RR showed a progressively significant decrease that corresponded with the increase in breathing rates; this phenomenon was not evident as far as TP–SBP was concerned ($P = 0.09$).

The respiratory component of the RR and SBP fluctuations also showed a significant reduction in concomitance with the increases in the respiratory rates (Table 1).

In all of the studied volunteers it was possible to calculate the gain between RR and systolic blood pressure signals. The gain assessed by means of the α index (Table 2 and Fig. 3), the Novak's CRI and the Bode plot (Table 2 and Fig. 4) showed a similar trend: a significant reduction

Table 1
Effects of breathing rate on cardiovascular variables

	Breathing rate		
	6/min ($n = 14$)	10/min ($n = 14$)	16/min ($n = 14$)
Time domain analysis			
Mean RR interval, ms	846 ± 124	843 ± 136	824 ± 144
ΔRR, ms	224 ± 137	166 ± 107	123 ± 55[a]
Mean systolic pressure, mmHg	120 ± 12	120 ± 9	121 ± 9
Mean diastolic pressure, mmHg	65 ± 7	65 ± 9	65 ± 6
Spectral analysis			
TP–RR, ln ms^2	8.6 ± 0.9	7.9 ± 0.9[a]	7.3 ± 0.8[ab]
TP–SBP, ln $mmHg^2$	3.3 ± 0.7	3.0 ± 0.4	3.0 ± 0.7
RR_{Resp}, ln ms^2	8.3 ± 0.9	7.3 ± 1[a]	6.1 ± 1.1[ab]
RR_{Resp}, Hz	0.1 ± 0.002	0.17 ± 0.01	0.26 ± 0.009
SBP_{Resp}, ln $mmHg^2$	2.4 ± 0.7	1.8 ± 0.5[a]	1.2 ± 0.8[ab]
Cross-spectral analysis			
RR-RESP			
K^2	0.9 ± 0.02	0.9 ± 0.02	0.9 ± 0.09
RR–SBP			
K^2	0.98 ± 0.009	0.97 ± 0.01	0.96 ± 0.02
Φ, degree	−43 ± 17	−32 ± 19[c]	−23 ± 14[a]

ΔRR = difference between the longest minus the shortest RR interval; TP–RR = total power of RR interval spectrum; TP–SBP = total power of the systolic blood pressure spectrum; RR_{Resp} = respiration-related component of the RR interval spectrum; SBP_{Resp} = respiration-related component of the systolic blood pressure spectrum; RR-RESP = cross-spectral analysis between RR and respiratory signals; K^2 = squared coherence function; RR–SBP = cross-spectral analysis between RR and systolic blood pressure signals; Φ = phase.
[a] $P < 0.01$ vs. 6/min; [b] $P < 0.01$ vs. 10/min; [c] $P < 0.02$ vs. 6/min.

Table 2
Values of gain at the three breathing rate

	Breathing rate		
	6/min ($n = 14$)	10/min ($n = 14$)	16/min ($n = 14$)
α index, ms/mmHg	21.3 (14.9–27.8)	17.6 (12.7–22.5)	13.1 (9.3–16.9)
CRI, ms/mmHg	7.9 (5.6–10.1)	6.5 (4.9–8.1)	4.9 (3.6–6.2)
Bode plot (decibels)	51.4 (46.9–55.9)	47.8 (42.6–53.1)	42.4 (36.9–48.1)

Values are mean (95% confidence interval).
CRI = cardiorespiratiry index.

in the values of the parameters obtained at a breathing rate of 6/min compared with those obtained at a breathing rate of 16/min. The phase lag between RR and SBP was always negative, and showed a significant reduction with the increases in respiratory rates (Fig. 3).

3.2. Chronic β-adrenoceptor blockade

As expected, β-adrenoceptor blockade lengthened the RR intervals (from 831 ± 75 to 1025 ± 100 ms at 6 breaths/min, from 832 ± 68 to 995 ± 76 ms at 10 breaths/min and from 799 ± 80 to 984 ± 90 ms at 16 breaths/min; $P < 0.001$), and decreased the systolic pressure (from 122 ± 10 to 110 ± 15 mmHg at 6 breaths/min, from 120 ± 12 to 109 ± 11 mmHg at 10 breaths/min and from 121 ± 9 to 110 ± 13 mmHg at 16 breaths/min; $P < 0.01$). The K^2 between RR interval and SBP oscillations was > 0.5 in all the subjects (0.96 ± 0.05 at 6 breaths/min, 0.98 ± 0.02 at 10 breaths/min and 0.98 ± 0.01 at 16 breaths/min). Chronic metoprolol treatment significantly increased the gain between oscillations in systolic pressure and RR interval at the three respiratory frequency periods (α index (95% confidence interval):

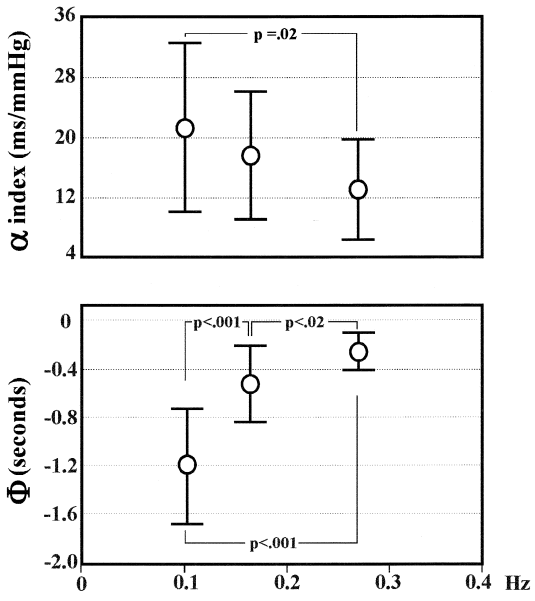

Fig. 3. Effects of breathing rate on the gain (α index; in top panel) and phase (Φ; bottom panel) relationships between respiratory RR interval and systolic blood pressure fluctuations. The higher the frequency of respiration, the smaller the α index and the Φ lag.

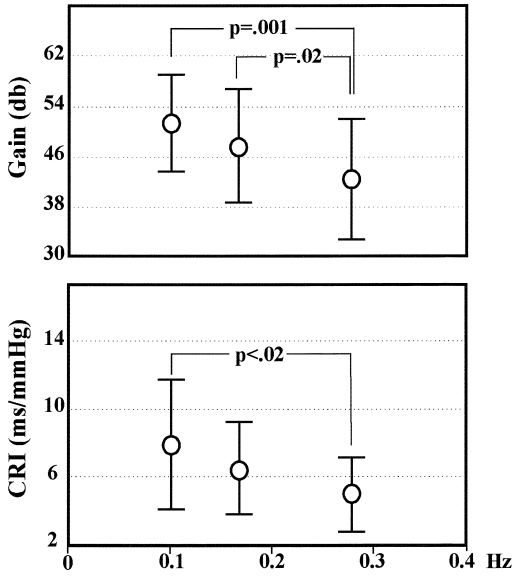

Fig. 4. Effects of breathing rate on the gain between RR and systolic pressure fluctuations in the respiratory band calculated in decibels (db) (top panel), and estimated as the cardiorespiratory index (CRI) (bottom panel). The values of both parameters decrease at higher respiratory frequencies.

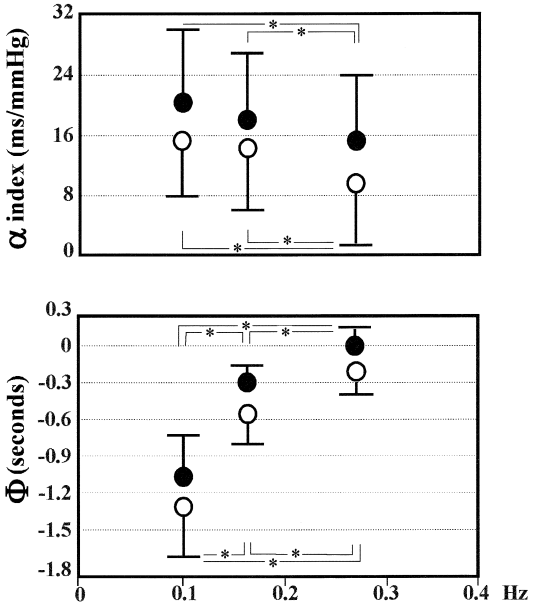

Fig. 5. The gain (α index; in top panel) and the phase (Φ; bottom panel) during three paced breathing sessions, before (○) and after (●) chronic metoprolol treatment in seven subjects. The β-adrenoceptor blockade always increased the gain ($P < 0.05$) and reduced the negativity of the phase ($P < 0.05$), but did not modify the frequency-dependent respiratory response. * $P < 0.05$.

from 15 ± 7 (8–23) to 20 ± 9 (10–30) ms/mmHg at 6 breaths/min, from 14 ± 8 (5–23) to 18 ± 9 (9–28) ms/mmHg at 10 breaths/min and from 9 ± 8 (1–18) to 15 ± 9 (6–25) ms/mmHg at 16 breaths/min; $P < 0.05$)) and shifted the phase (from -47 ± 14 to -40 ± 14 degrees at 6 breaths/min, from -35 ± 15 to -20 ± 9 degrees at 10 breaths/min and from -19 ± 14 to -3 ± 14 degrees at 16 breaths/min; $P < 0.05$), but did not modify the relationship found before treatment between the respiratory rate and either the gain or phase (Fig. 5).

4. Discussion

The main result of the present study is the finding that different breathing frequencies are capable of modifying the relationships between the oscillations in heart rate and systolic blood pressure.

The effect of respiration on sinus rhythm has been widely investigated since Angelone and Coulter [10] first described the frequency-dependent nature of RSA. The present study confirms the observation made much earlier by Fredericq (in 1882) that RSA decreases as breathing rate increases, as is shown by the changes in ΔRR and the power of RR_{Resp}. In agreement with Grossman et al. [2], who considered these two parameters as equivalent, we found a high correlation between the peak–valley and respiratory component of RR power spectrum during each phase ($r = 0.87$, $P < 0.001$ at 6 breaths/min, $r = 0.92$, $P < 0.001$ at 10 breaths/min and $r = 0.81$, $P < 0.001$ at 16 breaths/min). The peak–valley is easy to implement and provides quantitative information about RSA; however, in our study, the time domain measurements showed a respiration-related difference that was statistically significant only when the breathing rate of 6 breaths/min was compared with that of 16 breaths/min.

4.1. Breathing rate and spectral parameters

We have demonstrated that the rate of breathing greatly affects RR variance, a result that does not depend on its effect on the RR intervals because the increase in mean heart rate was only slight and not statistically significant. This finding is in accordance with that of Brown at al. [24], but not with those of Novak et al. [17] or Ahmed at al. [25], who found a significant increase in heart rate as the rate of breathing increases.

As the breathing rate can modify total power, controlling breathing is a necessary condition when the effect of drugs or manoeuvres on total power are under evaluation.

Breathing rate did not affect mean systolic blood pressure values nor the total power of systolic blood pressure oscillations; on the other hand, the respiratory-related component of systolic blood pressure oscillations was significantly affected by changes in breathing rate [13,16–18].

4.2. Effects of different breathing rates on the relationships between heart rate and systolic blood pressure oscillations

Previous studies have indicated that respiration greatly affects cardiovascular fluctuations, thus suggesting that it may be inappropriate to use the RR interval power and/or SBP power if breathing rates are neither measured nor controlled [13,15,24]. In the present study, we only evaluated the α index in the respiratory band at different breathing rates, which makes it possible to analyse the inter-relationships between RR and SBP fluctuations while taking respiratory activity into account. Analysis showed that the coherence of the three signals evaluated during controlled respiration was good in all of the subjects ($K^2 > 0.75$ in RR–RESP and $K^2 > 0.9$ in RR–SBP), a finding that makes it possible to speculate that controlled respiration is the best way of evaluating the relationships occurring in the cardio-respiratory system.

The gain between heart rate and SBP variabilities was calculated by means of the cardiorespiratory index and gain–frequency response (Bode plot), as well as by means of the α index. All of these parameters showed a frequency-dependent response at the different breathing rates, with system gain decreasing as the respiratory rate increased. In particular, all of them showed a significant reduction between a breathing rate of 6/min and that of 16/min.

Similar results were obtained using the CRI, the index suggested by Novak [17] as a means of correcting the RR interval and SBP oscillations for their respective mean values. The CRIs we obtained are similar to those of Novak, although we found a steeper decrease at the highest frequencies. On the other hand, Saul et al. did not find any frequency-dependent phenomenon during broad-band breathing in the 0.1–0.3 Hz range on the magnitudes and phase for transfer functions between heart rate and arterial blood pressure fluctuations (cf. Fig. 8B of Ref. [18]).

Our findings are in accordance with those of Eckberg [12], who documented a reduction in baroreflex responsiveness to a neck suction technique during rapid breathing.

Respiratory rate seems to play a major role in the frequency-dependent phenomenon of baroreflex control: previous studies designed to evaluate the α index without controlling the respiratory rate found either no difference in the values recorded in the low and high frequency bands [7], or a higher value at high frequency [20].

Another interesting finding of the present study is the fact that, at all three paced breathing rates, the phase between the RR interval and systolic blood pressure was negative, which we interpret as being suggestive of a baroreflex link: pressure changes provoke RR interval changes with a time delay, in accordance with both De Boer's hypothesis [4] and the results of Pagani et al. [7]. When the breathing rate increases, the lag between the two signals decreases from 1.2 s (at 0.1 Hz) to 0.25 s (at 0.27

Hz) (Fig. 3). The time of the phase lag between the RR interval and systolic blood pressure in the high frequency band (which explores the parasympathetic system) [4,24] is similar to the conduction time of the baroreceptor–cardiac reflex arc (0.24 s) found by Eckberg [26] in his study of young subjects using the neck suction technique. On the other hand, this value is lower than that found by Pagani et al. (0.37 s) in normotensive subjects of 41 years of age during uncontrolled respiration [7], and that found by Sopher et al. in normal subjects aged 46 years (0.35 s) using the neck suction technique [27]. These results make it possible to hypothesize that the phase obtained from the cross-spectrum analysis of RR and systolic blood pressure in the high-frequency band may be an estimate of the baroreceptor–cardiac reflex vagal arm. On the basis of our own results and those of others, a direct relationship seems to exist between baroreflex latency and age, although this is not accepted by some authors [28]. Furthermore, phase lag may be modified by other factors such as the influence of RR interval on blood pressure. Our results contrast with those obtained by Taylor et al. [29] in normal subjects during controlled breathing at 15 breaths/min in a supine position, where SBP variations were found to follow those in the RR interval.

4.3. Sympathetic contribution

As the non-neural and mechanical effects of RSA are negligible at rest [30], these results make it possible to hypothesize that the respiratory inter-relationships between RR and SBP in the low frequency band are governed by the sympathetic and vagal contribution, but those in the high frequency band (near 0.27 Hz) are primarily governed by the vagal arm of baroreflex control (De Boer's model). Therefore, the different contributions of sympathetic activity could explain the effect of different respiratory rates on the RR–SBP relationship. However, this hypothesis is not supported by our data, as β-adrenoceptor blockade did not modify the effect that different breathing rates had on the relationship between RR and systolic blood pressure oscillations, thus minimizing the contribution of sympathetic activity to the frequency-dependence of the gain and phase.

The frequency-dependence of the spectral gain and phase of the relationship between RR and SBP variabilities could be explained by non-autonomic mechanisms. A lower breathing rate could cause greater cardiac output oscillation and increase SBP oscillations; as a consequence, more sensitive baroreflex control may be necessary in order to buffer the increased SBP variability.

Another possible explanation of our finding is that increasing the breathing rate could cause differences in the central modulation of the baroreceptor efferent pathway, at least as far as the vagal arm is concerned.

However, our study design does not allow us to confirm or refute these hypotheses, which need to be tested in an ad hoc designed study.

4.4. Limitations of the study

Tidal volume was not measured, in order to allow the subjects to control their acid–base balance; we therefore do not know whether the minor changes in tidal volume that may occur at different breathing frequencies could have affected our findings. However, it has been previously found that changes in tidal volume are less important than breathing frequency [11].

Another limitation is that, although voluntarily paced breathing concentrates the power in a narrow frequency band and therefore increases the reliability of spectral estimates by providing a better estimate of SBP–RR gain, it may directly influence the relationship between RR and systolic pressure variability [31]; however, this effect was present in all the three studied phases.

Finally, we studied the cardiorespiratory system by means of cross-spectral analysis and, although this closed-loop model has been widely used for this purpose [4,8,14,18,29,32], it offers only a rough index of time relationships and does not allow any precise analysis of the effect of each parameter on the others.

5. Conclusions

The respiratory rate modulates the inter-relationship between the RR interval and SBP variabilities: the higher the breathing rate, the smaller the gain and the shorter the phase between the two. This is also true after β-adrenoceptor blockade, thus suggesting that the sympathetic drive is not involved. The spontaneous baroreflex assessed by means of spectral analysis is therefore dependent upon respiratory frequency.

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