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Gain and coherence estimates between respiration and heart-rate: Differences between inspiration and expiration

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ABSTRACT

The interaction of respiration and heart-rate variability (HRV), leading to respiratory sinus arrhythmia (RSA) and, in the inverse direction, cardioventilatory coupling has been subject of much study and controversy. A parametric linear feedback model can be used to study these interactions. In order to investigate differences between inspiratory and expiratory periods, we propose that models are estimated separately for each period, by finding least mean square estimates only over the desired signal segments. This approach was tested in simulated data and heart-rate and respiratory air flow signals recorded from 25 young healthy adults (13 men and 12 women), at rest, breathing spontaneously through a face mask for 5 min. The results show significant differences ($p < 0.05$) between the estimates of coherence obtained from the whole recording, and the inspiration and expiration periods. Simple and causal coherence from respiration to HRV was higher during inspiration than expiration. The estimates of gain also differed significantly in the high frequency (HF) band (0.15–0.5 Hz) between those obtained from the whole recording, and the inspiratory and expiratory periods. These results indicate that a single linear model fitted to the whole recording neglects potentially important differences between inspiration and expiration, and the current paper shows how such differences can be estimated, without the need to control breathing.

1. Introduction

The autonomic control of the cardiovascular system has been extensively studied by techniques that assess heart rate variability (HRV). Clinical risk evaluation and the relationship between psychological processes and physiological functions have been commonly addressed in these studies (Berntson et al., 1997). However, the evaluation of autonomic cardiovascular control by means of the HRV is still subject of some controversy (Parati et al., 2006; Beda et al., 2007).

HRV is modulated by respiration, a phenomenon called respiratory sinus arrhythmia (RSA), which is responsible for most of the variability of the heart rate (HR). RSA has been used to quantify vagal activity and it has been related to prognosis of cardiovascular health (Camm et al., 1996; Berntson et al., 1997; Parati et al., 2006; Beda et al., 2007). However, not only the autonomic tone influences RSA, but also other factors including differences in breathing parameters between individuals in respiratory frequency, amplitude, and the relative length of inspiration and expiration periods can affect the level of RSA (Brown et al., 1993; Strauss-Blasche et al., 2000; Cammann and Michel, 2002; Yasuma and Hayano, 2004).

In previous studies, paced breathing has often been used to standardize these periods and investigate the effect of their variations (Stark et al., 2000; Grossman et al., 2004). It was noted that rapid inspiration leads to increased RSA (Strauss-Blasche et al., 2000), whereas rapid expiration does not have such an effect. Evidence that baroreflex responsiveness is different between inspiration and expiration (Eckberg, 2003) further reinforces the relevance of considering these two periods separately for investigations of HRV modulation. A protocol in which subjects are breathing spontaneously seems a more desirable approach than paced breathing, for two main reasons: paced breathing leads to physiological repercussions that may confound in the comprehension of RSA (Ritz, 2009); also, it impacts on the ability to carry out other physical or mental challenges at the same time and thus greatly restricts the scenarios that can be investigated.

The interaction between respiration and HRV has been extensively investigated in previous works (Porta et al., 2012). The objective of this study is to adopt a similar approach, but estimating the transfer function separately for the inspiration and expiration periods. Specifically, we present a method that can provide such separate estimates from the same recording and test for differences in the coupling between respiration and HRV in these two periods on a set of data recorded from healthy adult volunteers at rest, breathing spontaneously.

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2. Methods

In the following, first the model-based methods for estimating the coherence and gain will be reviewed (based on Porta et al., 2002) followed by a description of how this can be adapted to permit separate estimates during only the inspiratory and expiratory periods.

2.1. Coherence, causal coherence and autoregressive modeling with missing samples

The coherence function expresses the synchrony between the two signals x_1 and x_2, and is defined as:

$$\gamma^2_{1,2} = \frac{|S_{12}(f)|^2}{S_{11}(f)\cdot S_{22}(f)} \quad (1)$$

where $S_{12}(f)$ is the cross-spectrum, and $S_{11}(f)$ and $S_{22}(f)$ are the auto-spectra of the analyzed signals, respectively (Bendat and Piersol, 1986; Baccala and Sameshima, 2001). Initially developed for economic science, the Granger concept of causality aims to assess causality in relationships between the two signals by assessing the contribution the second signal makes to predicting the next sample of the first, over and above the prediction achieved from only previous samples of the latter (Granger, 1969). Applying the Granger causality concept to coherence leads to causal coherence, which aims at quantifying the level at which two signals are functionally connected (Baccala and Sameshima, 2001). Granger causality (Granger, 1969) is probably the most commonly used approach in related studies of the cardiovascular system, (Porta et al., 2002; Faes et al., 2004; Faes and Nollo, 2006), though there are several other alternatives, such as symbolic coupling traces (Wessel et al., 2011) and mixed state analyses (Wiesenfeldt et al., 2001). Granger causality has also previously been used in the context of the cardio-respiratory interactions, for example in Porta et al. (2002), Faes et al. (2004), and Faes and Nollo (2006).

In order to obtain the (Granger) causal coherence, a multivariate AR model is implemented that represents a closed loop model as shown in Fig. 1 (Porta et al., 2002).

This is defined by the following equation system:

$$x_1[t] = \sum_{k=1}^{n} a_{1,1}(k)x_1[t-k] + \sum_{k=1}^{n} a_{1,2}(k)x_2[t-k] + w_1[t] \quad (2)$$

$$x_2[t] = \sum_{k=0}^{n} a_{2,1}(k)x_1[t-k] + \sum_{k=1}^{n} a_{2,2}(k)x_2[t-k] + w_2[t] \quad (3)$$

In our study, x_1 represents the HRV signal and x_2 the respiratory flow signal, w_1 and w_2 are the independent white Gaussian noises, with zero mean and variances of λ_1 and λ_2 respectively, and n is the model order, which is here taken to be equal for all filters. The coefficients of the model are represented by $a_{i,j}(k)$, where i refers to the output and j the input signal, and k is the lag. It should be noted that here $a_{2,1}(0) = 0$ while $a_{1,2}(0) \neq 0$, imposing strict causality only in the $x_2 \rightarrow x_1$ direction but allows for instantaneous effects in the reverse pathway. A linear representation of the causal relationship from x_1 to x_2 is obtained by setting all the $a_{1,2}(k)$ coefficients to zero, and equivalently, to obtain the x_2 to x_1 relationship, the $a_{2,1}(k)$ coefficients are set to zero. This way, feedback effects from the other signal are disregarded and the causal effects are obtained. The auto and cross-spectral density functions can then be calculated, after z-transformation (Porta et al., 2002) as:

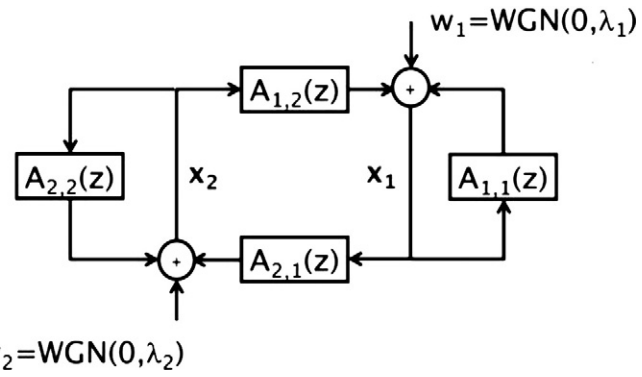

Fig. 1. Closed loop model representation used to model the relationship between HRV and respiration, WGN indicates white Gaussian noise.

$$S_{11}(f) = |\Delta(z)|^2 \cdot \left[\left|1-A_{2,2}(z)\right|^2 \cdot \lambda_1^2 + \left|A_{1,2}(z)\right|^2 \cdot \lambda_2^2\right] \quad (4)$$

$$S_{22}(f) = |\Delta(z)|^2 \cdot \left[\left|A_{2,1}(z)\right|^2 \cdot \lambda_1^2 + \left|1-A_{1,1}(z)\right|^2 \cdot \lambda_2^2\right] \quad (5)$$

$$S_{12}(f) = |\Delta(z)|^2 \cdot \left[\left(1-A_{2,2}(z)\right)\cdot A_{2,1}\left(z^{-1}\right)\cdot \lambda_1^2 + A_{1,2}(z)\cdot\left(1-A_{1,1}\left(z^{-1}\right)\right)\cdot \lambda_2^2\right] \quad (6)$$

where

$$|\Delta(z)|^2 = \left(\left(1-A_{1,1}(z)\right)\cdot\left(1-A_{2,2}(z)\right) - A_{1,2}(z)\cdot A_{2,1}(z)\right)^{-1} \quad (7)$$

and

$$A_{i,j} = \sum_{k=0}^{n} a_{i,j}(k)z^{-k} \quad (8)$$

with $i,j = 1$, and 2 and $z = e^{j\cdot 2\cdot\pi\cdot f/f_s}$, f is the frequency, and f_s the sampling frequency.

The simple (bidirectional) coherence can then be calculated by directly inserting Eqs. (4), (5) and (6) in Eq. (1), and causal coherences in a similar manner after removing the feedback path (Porta et al., 2002):

$$\gamma^2_{i\rightarrow j}(f) = \gamma^2_{i,j}(f)|_{A_{i,j}(z)=0} \quad (9)$$

with $j,i = 1$, and 2 and the gain as

$$G_{i\rightarrow j}(f) = \left|\frac{A_{j,i}(f)}{1-A_{j,j}(f)}\right| \quad (10)$$

with $j,i = 1$, and 2.

In order to calculate the coherence (causal or not) and the gain for only the inspiratory (or expiratory) phase, we now mark all the samples during the expiratory (or inspiratory) phase as 'missing' by replacing them with Not-a-Number (NaN). This leads to signals with gaps (see Fig. 2) and thus parameter estimation methods need to be adapted accordingly. The coefficients of the AR model were estimated by the least squares method applied over the available (remaining) samples (Simpson et al., 2001; Simpson et al., 2005). This may be illustrated for the simple example for a univariate AR model shown in Eq. (11).

$$x[n] = \sum_{i=1}^{M} a_i x[n-i] + \varepsilon[n] \quad (11)$$

and order M = 3, with sample x[4] missing. As shown in Eq. (12), the error ε can only be calculated for samples ε[3], ε[8], ε[9] and ε[10]. In all other lines, either the left side of the equation or the matrix product is NaN, and hence the residual ε[i] is also a NaN. The parameters a_1, a_2, and a_3 are then estimated by minimizing the mean-square

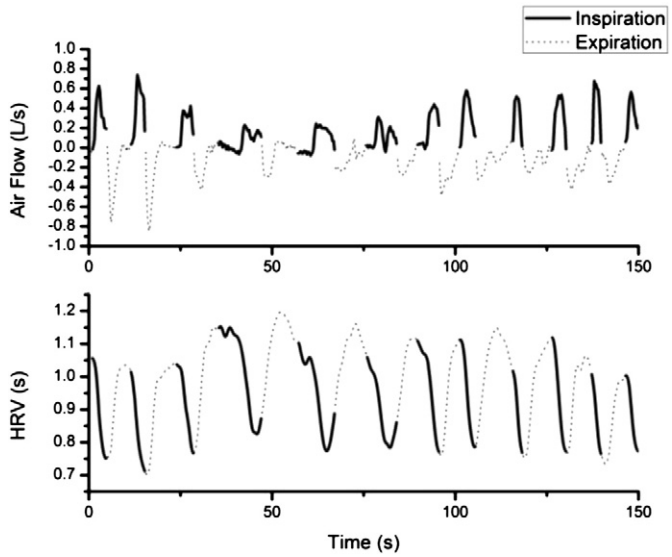

Fig. 2. One example of HRV signals with gaps for inspiration and expiration, respectively.

error only over the remaining four 'good' samples available ($\varepsilon[3]$, $\varepsilon[8]$, $\varepsilon[9]$ and $\varepsilon[10]$):

$$\begin{bmatrix} x[1] \\ x[2] \\ x[3] \\ NaN \\ x[5] \\ x[6] \\ x[7] \\ x[8] \\ x[9] \\ x[10] \end{bmatrix} = \begin{bmatrix} x[0] & NaN & NaN \\ x[1] & x[0] & NaN \\ x[2] & x[1] & x[0] \\ x[3] & x[2] & x[1] \\ NaN & x[3] & x[2] \\ x[5] & NaN & x[3] \\ x[6] & x[5] & NaN \\ x[7] & x[6] & x[5] \\ x[8] & x[7] & x[6] \\ x[9] & x[8] & x[7] \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ a_3 \end{bmatrix} + \begin{bmatrix} NaN \\ NaN \\ e[3] \\ NaN \\ NaN \\ NaN \\ NaN \\ \varepsilon[8] \\ \varepsilon[9] \\ \varepsilon[10] \end{bmatrix} \quad (12)$$

The use of gaps (missing samples) in the data, represented by NaN, thus permits the analysis to focus on inspiration or expiration only, across the whole recording. It should be emphasized that in this analysis the data from before and after the gaps are not concatenated, which would lead to artificial discontinuities in the data. Setting these samples to zero is evidently also not permitted, as it would introduce bias in the estimates. An important consequence of the above procedure is that with each sample that is NaN on the input, a further n (the model order) samples are required, before the output can again be predicted, leading to an increased loss of useful samples when there are many small gaps, rather than a few larger ones. On the other hand, when a sample is missing at the output, this only leads to the loss of one sample in calculating the prediction error. While in the current work the gaps in both input and output signal are identical (as they represent the inspiratory or expiratory periods), the method itself does not impose such constraints.

2.2. Data collection and preprocessing

The experimental data considered in this work is part of a database collected in the Biomedical Engineering Program at COPPE/Federal University of Rio de Janeiro, Brazil. Respiratory air flow and ECG signals were recorded from a total of 25 volunteers (13 men and 12 women), non-smokers, with no known cardiorespiratory disorders, at rest, breathing spontaneously through a face mask to measure respiratory air flow with a pneumotachograph. ECG was also recorded simultaneously. Further details on data acquisition protocol and data preprocessing are provided in Beda et al. (2007). R–R interval time series and flow signal (the latter acquired with sampling frequency of 1000 Hz) were resampled at 4 Hz, using cubic *splines* to interpolate R–R intervals, and visually inspected prior to analysis. Resampling was required to allow alignment of samples in the (uniformly sampled) respiratory signal with the (irregular) heart-beats. Both signals were then hi-pass filtered with a cutoff frequency of 0.05 Hz (2nd order Butterworth, applied in the forward and reverse direction to obtain zero lag). The aim of this was to avoid the parametric model in Fig. 1 being fitted primarily to the large very slow fluctuations of the signals rather than those of interest (0.05–0.5 Hz).

Inspiratory and expiratory periods were identified from the raw flow signal, using an automatic algorithm based on zero crossings and removal of erroneous cycles (small fluctuations around zero flow that do not constitute respiratory cycles), followed by manual checks. All recordings processed were 5 min in duration.

2.3. Simulations

In order to test the methods, three sets of simulations were carried out. These aim to assess the bias and random errors in coherence estimates resulting from introducing gaps in the signals, either randomly located (i.e. unrelated to respiration, first two simulations) or corresponding to the inspiration (or expiration) periods in the flow signal (third simulation).

First the system proposed by Porta et al (2002) was employed, comparing conventional estimates of gains and coherence with those obtained when introducing gaps (i.e. sequences of NaN) in the data to simulate inspiration (or expiration). The gaps were introduced assuming a constant inspiratory and expiratory period of 2 and 3 s respectively (8 and 12 samples, respectively). The synthetic system is described by the following equations:

$$y_1[k] = ky_2[k-2] + w_1[k] \quad (13)$$

$$y_2[k] = \alpha y_1[k] + w_2[k] \quad (14)$$

where w_1 and w_2 are the uncorrelated Gaussian white noise sources with variances γ and δ respectively.

One thousand pairs of signals were generated with $\alpha = 0.7$ and $k = -0.7$, $\gamma = 1$ and $\delta = 0.2$. The model coefficients and then the coherence were estimated as described in Sections 2.1 and 2.4, first for all the data and then with the inspiratory (or expiratory) samples replaced with NaNs.

In order to assess the effect of adding gaps to the coherence estimates of our experimental data, another set of simulations was performed, based on the model coefficients identified from one of the recorded signals according to the model in Fig. 1 (subject #11, see Sections 2.1 and 2.4 for details of the model identification). First we simulated 100 pairs of signals lasting 1200 samples using white noise inputs (w_1 and w_2), to simulate air flow and R–R intervals. For each pair we estimated the coherence, before and after replacing the inspiratory or expiratory periods (as identified in the original data) with NaNs. For comparison, also the Discrete Fourier Transform (DFT) based coherence estimate (with 40 s windows, 50% overlapped) was calculated (without gaps only, as gapped data cannot be processed by DFTs). We then calculated the mean as well as standard deviations of the coherence estimates, across the 100 sets of simulated signals.

In the previous simulations, the gaps are unrelated to the simulated signals. However, in the recorded data, the gaps are defined by the air flow signal itself and this may impact on estimated coherences. The final simulation aimed at investigating this impact. Thus the recorded respiratory signal from one subject (again #11) was used, and only the HRV signal was simulated, now using only the feedforward path of the model (from air flow to HRV) and adding noise. The model parameters and the spectrum of the noise were both based on the estimates obtained from the same recording.

2.4. Experimental data analysis

For each subject, the coefficients of the model defined in Section 2.1 were identified. From a preliminary analysis, a model order of 4 was selected for identification, since it provided the best overall performance according to Akaike's criterion (Porta et al., 2002; Faes et al., 2004; Faes and Nollo, 2006).

From the estimated model coefficients, the coherence (simple and directed) and gain functions were calculated, and their average value in the low frequency band (LF: 0.05–0.15 Hz) and high frequency band (HF: 0.15–0.5 Hz) was used in statistical comparison.

The effect of using either all, inspiratory, or expiatory data for parameter estimation was tested using Friedman's tests, followed by Tukey's post-hoc analysis. Results were considered statistically significant when $p < 0.05$.

3. Results

3.1. Simulations

The mean of the causal coherence estimates agrees with the expected values of $y_1 \rightarrow y_2 = 0.84$, and $y_2 \rightarrow y_1 = 0.3$. Similar results were obtained for estimates during inspiration and expiration only, though with larger random estimation errors, as might be expected, as the amount of available data is of course greatly reduced. In all cases (continuous and gapped data), the correct value of coherence (given the model) was between the 2.5th and 97.5th percentile of the distribution of estimates. The simulations thus indicate that including the gaps does not distort the coherence estimates.

The second set of simulations shows very good agreement between the three model-based estimates of simple coherence. These estimates also agree well with the DFT-based estimate in the LF and HF bands, except at higher frequencies, where the latter shows a larger positive bias. Variances of estimates were also larger for the inspiratory and expiratory segments than for the whole signal (not shown), in accordance with the reduced amount of data available.

When the recorded (rather than simulated) respiratory signal was used, the estimates no longer agree, as shown in Fig. 3B, with the estimates during inspiration showing a higher peak, that occurs at a higher frequency, than those during the expiratory period. It may be noted that the ratio of inspiratory to expiratory period was 0.8, in this recording. Similar results were also obtained when simulating other recordings.

3.2. Experimental data

The following notation will be adopted, referring to the model identification: γ^2: simple coherence; $\gamma^2_{i \rightarrow j}$ directed coherence with signal i as the input and j as the output; $G_{j \rightarrow i}$: gain of the $j \rightarrow i$ transfer function in the model; ALL — the use of all data (no gaps): INS — the use of inspiratory period only; EXP — the use of expiratory period only. The average respiratory frequency for each subject is shown in Fig. 4. The mean respiratory frequency among all subjects was 12.4 (±3.6 std. dev.) breaths per minute (bpm).

Fig. 5 shows the average simple coherence, directed coherence, and gains of the RESP → HRV and HRV → RESP transfer functions, estimated using either all, inspiratory or expiratory periods. Table 1 reports the average values of coherence and gain estimates in the LF and HF bands. The choice of the period used for model identification (ALL, INS, or EXP) has a significant effect on coherence estimates. Coherence was significantly higher for inspiration than expiration for all three estimators in both frequency bands, except for $\gamma^2_{HRV \rightarrow RESP}$. Furthermore, causal coherence estimates from respiration to HRV and the reverse path were significantly different ($\gamma^2_{RESP \rightarrow HRV}$ estimations were higher $p < 0.001$ — Wilcoxon test). Finally, the gains in HF and LF were significantly different to each other (Friedman, $p < 0.001$, with one test each for simple and the causal coherences, with periods as a second factor).

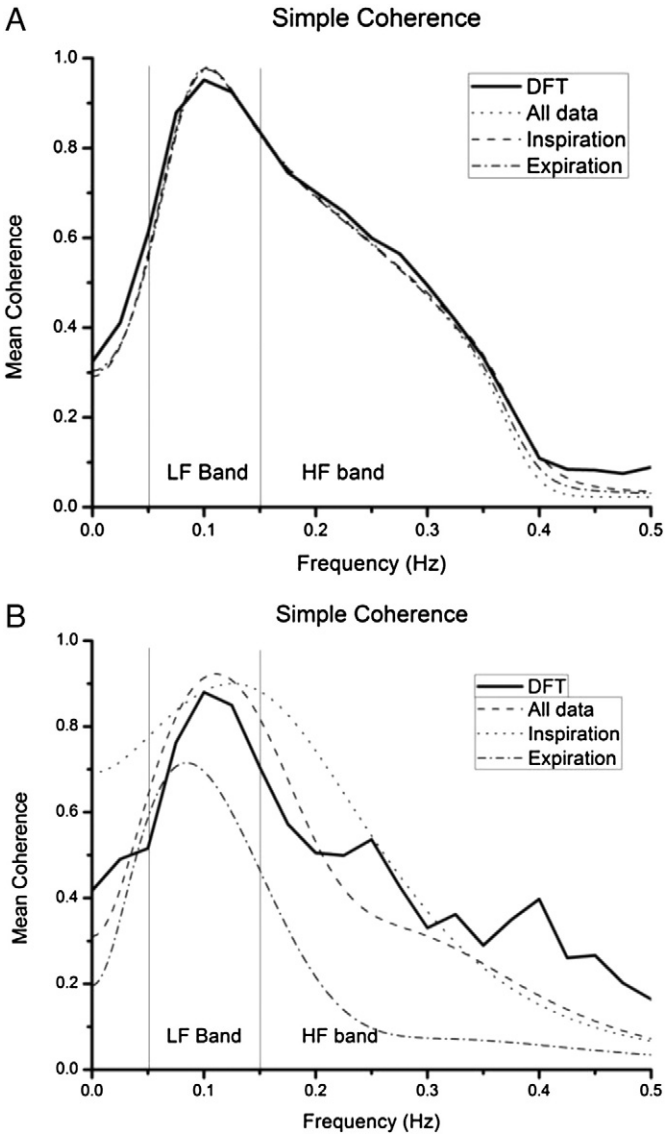

Fig. 3. A) Mean coherence estimates from 100 pairs of simulated signals, showing good agreement between estimates from the whole recording as well as the inspiratory and expiratory periods. The non-parametric estimate (DFT) also gives very similar results up to 0.5 Hz. B) Mean coherence estimates from 100 simulated HRV signals, using recorded respiratory flow signals. The coherence for the shorter inspiratory period is larger and at a higher frequency than that for the expiratory period.

We then also plotted the mean coherence in the LF as a function of respiratory frequency, and this is shown in Fig. 6. Clearly (and as expected) conventional coherence increases as respiration shifts towards the low frequency range (correlation coefficient $r = -0.76$, $p < 0.001$), and this effect is reduced for estimates obtained either only in inspiration or only expiration ($p < 0.05$, randomization test). In HF, coherence increases with respiratory frequency ($r = 0.80$, $p < 0.001$), and this effect is again less pronounced ($p < 0.05$, randomization test) for estimates using only the inspiratory or expiratory period.

4. Discussion and conclusions

To the best of our knowledge, the application of coherence estimates with gapped data has not previously been reported for the study of respiratory–HRV interactions, and more generally has not been widely exploited. In the study of cardio-respiratory interactions,

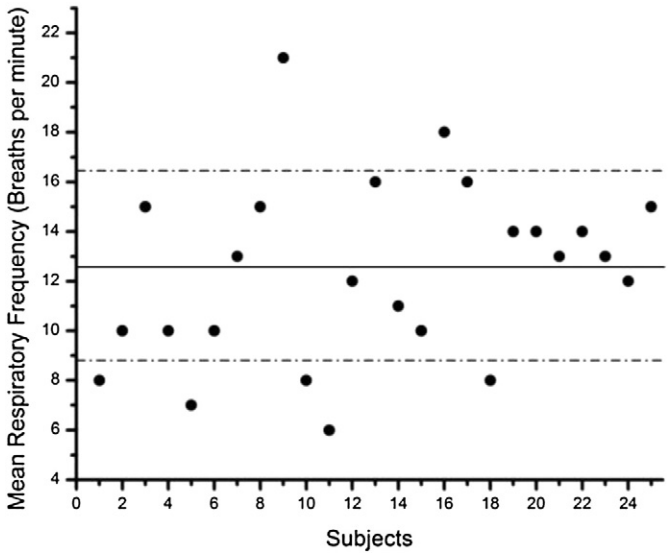

Fig. 4. Mean respiratory frequency (breaths per minute) for the 25 subjects. The solid line shows mean respiratory frequency and the dashed lines ± one standard deviation.

Table 1
Mean (st.dev) for the values of coherence, causal coherence and gain estimates for all data, inspiration and expiration.

	LF		HF	
γ^2				
ALL	0.41 (0.15)		0.53 (0.16)	
INS	0.65 (0.06)	*■◆	0.45 (0.20)	*▲◆
EXP	0.37 (0.15)		0.26 (0.14)	
$\gamma^2_{RESP\rightarrow HRV}$				
ALL	0.41 (0.02)		0.41 (0.12)	
INS	0.51 (0.01)	*◆	0.41 (0.14)	*▲◆
EXP	0.31 (0.02)		0.15 (0.05)	
$\gamma^2_{HRV\rightarrow RESP}$				
ALL	0.20 (0.08)		0.12 (0.06)	
INS	0.16 (0.03)	-	0.12 (0.01)	-
EXP	0.24 (0.08)		0.09 (0.07)	
$G_{RESP\rightarrow HRV}$ (s^2/L)				
ALL	0.19 (0.03)		0.07 (0.04)	
INS	0.23 (0.02)	*■◆	0.08 (0.03)	*▲◆
EXP	0.20 (0.05)		0.09 (0.06)	
$G_{HRV\rightarrow RESP}$ (L/s^2)				
ALL	2.45 (0.44)		4.86 (0.81)	
INS	1.92 (0.47)	-	5.41 (1.35)	*▲◆
EXP	2.07 (0.15)		1.44 (0.16)	

Statistically significant for: *Friedman test for overall effect ($p < 0.05$); Tukey´s post-hoc analysis ($p < 0.05$): ■ ALL vs INS; ▲ ALL vs EXP; ◆ INS vs EXP.

most commonly a linear, time-invariant model is assumed, that is applied across the whole recordings, not allowing for any differences between the inspiratory and expiratory periods. The current method overcomes this as it permits analysis of inspiration and expiration periods separately, i.e. inspiration and expiration may now display different input–output relationships. The current method also does not require coherent averaging of respiratory cycles that was used in some previous studies (Stark et al., 2000; Grossman et al., 2004) and thus can exploit between cycle variability to provide a richer insight into RSA and cardioventilatory coupling (Tzeng et al., 2003), for example during spontaneous breathing. It provides a mean of analyzing the distinct effects of inspiration and expiration without the need to control breathing (e.g. fixed respiratory frequency), which can lead to confounding results (Cammann and Michel, 2002; Grossman et al., 2004).

The first two simulations clearly demonstrate that the coherence estimates from gapped data are robust, with mean values compatible with those from the whole recording, though with increased random errors, as expected from the reduced length of data used. The third simulation (using the recorded respiratory air flow signal) provides useful additional insights. The model and the noise-level are constant throughout the data, so it may at first seem surprising that mean coherence estimates now show quite distinct values for the inspiratory and expiratory periods. However, the inspiratory period is shorter than the expiratory one (with a ratio of inspiration to expiration of 0.8 in this recording, which is typical of the set of data and of

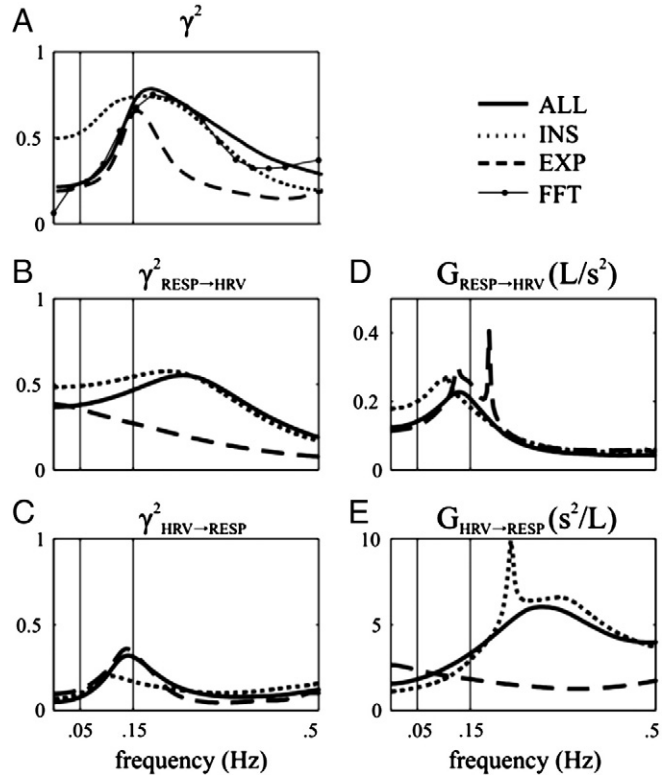

Fig. 5. Mean values of coherence estimates from using all data, just inspiration periods, or just expiration periods for: A) γ^2; B) $\gamma^2_{HRV\rightarrow RESP}$; C) $\gamma^2_{RESP\rightarrow HRV}$; D) $G_{HRV\rightarrow RESP}$; and E) $G_{RESP\rightarrow HRV}$.

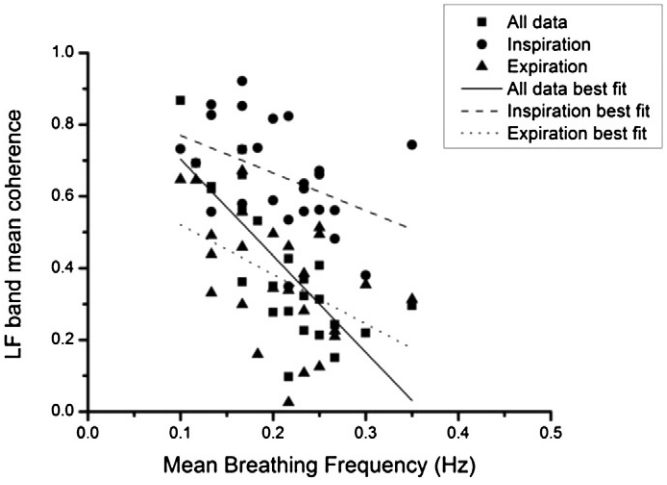

Fig. 6. Mean coherence in the LF range for each individual, estimated for ALL, INS and EXP. Coherences increase as the respiratory frequency drops, but this dependence is less pronounced when considering only the inspiratory or expiratory periods. Pearson r coefficients for all, inspiration and expiration data respectively: −0.76($p < 0.001$); −0.42($p = 0.03$); and −0.47($p = 0.01$).

spontaneous breathing). Furthermore, as the same volume of air is inhaled as is exhaled (this corresponds to the area under the respiratory flow curve), the average signal power is also higher. It is therefore not surprising that the peak coherence is higher and occurs at a higher frequency during inspiration than expiration. To confirm that these differences were indeed due to the characteristics of the subject's respiration rather than the algorithm, we then also randomized the gaps in the data, such that the number and duration of gaps and of the segments of 'good data' were maintained, but they followed each in a random order, without being synchronized to the respiratory activity. Now there was again little difference between the estimates from the two segments of the recording (results not shown). These results provide further confirmation that the estimator of coherence in the gapped data is robust, and underlines the fact that coherence depends on signal, as well as system characteristics. For example, when subjects change their respiratory frequency the peak of the coherence function would also shift (in accordance with theory, regardless of estimator), even if the physiological system maintained exactly the same transfer function between respiration and heart-rate (Porta et al., 2012). The proposed method was thus able to identify such shifts also between inspiration and expiration periods in the same recording.

The recorded signals show a very wide range of respiratory frequencies. The impact of respiratory frequency on coherence estimates is clearly shown in Fig. 6. The separate analysis of the inspiratory (expiratory) periods makes the spectrum independent of the duration of the expiratory (inspiratory) period. It is thus not surprising that the LF coherence estimates obtained from the inspiratory and expiratory periods are less dependent on respiratory frequency (determined by the sum of inspiratory and expiratory durations) than those obtained from the whole recording (Fig. 6). A similar effect, but less pronounced, was also observed in the HF range (result not shown).

As expected, the results showed that causal coherence from respiration → HRV is higher than in the inverse direction. The former refers to the well known respiratory drive on HRV taken as the primary mechanism for RSA, and the latter to the less well-established (and weaker) cardio-ventilatory coupling (Tzeng et al., 2003)

It is notable that coherence is consistently higher in inspiration than expiration ($p < 0.05$) for simple and causal coherence from respiration to HRV. This would suggest a tighter link between air flow and HRV during this phase, and is in agreement with previous work (Strauss-Blasche et al., 2000), where a rapid inspiration was noted to lead to increased HRV compared to baseline, whereas a rapid expiration did not, indicating that HRV is more sensitive to inspiratory than to expiratory parameters. The trend towards higher coherence during inspiration was observed at all respiratory frequencies (see regression lines in Fig. 6, with similar results for the HF band — not shown). It should be pointed out (see discussion above of the third simulation) that part of this higher coherence can probably be attributed to the increased power (shorter duration) of the inspiratory period (as shown in the simulation, Fig. 3) without necessarily implying changes in the system. Mean gains are however also significantly different between inspiration and expiration (except $G_{HRV \rightarrow RESP}$ in the LF range), indicating a change in the system.

Respiration is generally considered to dominate in the HF band, and higher coherences may thus be expected in that band — but that is not generally observed in Table 1. However, in our sample respiratory peaks were often close to or even below the border of 0.15 Hz (Beda et al., 2007). Furthermore, Fig. 6 clearly confirms the expected increase in LF coherence as respiratory rate decreases. This may partly be explained by the broad respiratory peak in coherence increasingly contributing to the LF mean, coupled with the known increase in R–R intervals at lower respiratory frequencies (Yasuma and Hayano, 2004). Furthermore, given the greater width of the HF band, it includes a larger portion of the tail of the peak and this may bias averages downwards in that band. With separate analyses of inspiration and expiration periods, the average respiratory frequency is not directly relevant and the already questionable use of 0.15 Hz as the cut-off between bands (Cammann and Michel, 2002), becomes even less justified.

It should also be noted that $G_{RESP \rightarrow HRV}$ and $G_{HRV \rightarrow RESP}$ are different between ALL, INS and EXP. The difference in gains obtained in the different segments provides a tantalizing indication that the estimates from the whole recording may be a mixture of quite distinct behaviors, and that greater insights into the underlying physiology might be obtained from considering the segments separately.

The least squares estimation method of coherence using available samples proved promising for RSA analysis to identify differences between respiratory periods in adults. A limitation however is that model orders must be lower than the duration of the inspiratory (and expiratory) periods. For example, if inspiratory (or expiratory) periods are represented by 12 samples, the model order cannot be superior to this, because there would be missing samples in every line of the regression matrix (see Eq. (12)) and the coefficients would not be estimated. Furthermore, after each missing sample, the model can only be applied once a further n samples (n is the model order, see Eqs. (2) and (3)) have passed — prior to that the output is Not-A-Number. Thus the amount of useful data is greatly reduced, when there are many short gaps, and model orders are high. In the current case the Akaike model order selection criteria indicated an order of four (for both the moving average and the recursive components) that satisfied this requirement. The successful prediction of HRV from respiration and the good match between coherence estimated from the DFT-based method (Welch — results not shown) suggests that the model used can capture the main features in the current data. However, the order is quite low and may not be adequate for other studies. Low orders may bias the estimates, with possibly complex interactions between model order selection and signal pre-processing (filtering). This requires further investigation. In addition, the current work considered air flow (as measured by the pneumotachograph), rather than volume which is more commonly used; further studies will assess result when using the latter.

The proposed method thus provides a new tool in the analysis of HRV that may help to overcome some current challenges. This initial study provided some promising new insights and encourages further investigations into cardio-respiratory interaction without the need for inspiration and expiration to be fitted by the same model.

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