# Influence of Respiration in the Very Low Frequency Modulation of QRS slopes and Heart Rate Variability in Cardiomyopathy Patients

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## Abstract

*This work investigates the very low frequency (VLF) modulation of QRS slopes and heart rate variability (HRV). Electrocardiogram (ECG) and respiratory flow signal were acquired from patients with dilated cardiomyopathy and ischemic cardiomyopathy. HRV as well as the upward QRS slope ($I_{US}$) and downward QRS slope ($I_{DS}$) were extracted from the ECG. The relation between HRV and QRS slopes in the VLF band was measured using ordinary coherence in 5-minute segments. Partial coherence was then used to remove the influence that respiration simultaneously exerts on HRV and QRS slopes. A statistical threshold was determined, below which coherence values were considered not to represent a linear relation.*

*7 out of 276 segments belonging to 5 out of 29 patients for $I_{US}$ and 10 segments belonging to 5 patients for $I_{DS}$ presented a VLF modulation in QRS slopes, HRV and respiration. In these segments spectral coherence was statistically significant, while partial coherence decreased, indicating that the coupling HRV and QRS slopes was related to respiration. 4 segments had a partial coherence value below the threshold for $I_{US}$, 3 segments for $I_{DS}$. The rest of the segments also presented a notable decrease in partial coherence, but still above the threshold, which means that other non-linearly effects may also affect this modulation.*

## 1. Introduction

Interactions between the parasympathetic and sympathetic nervous systems, have been largely studied and associated with high frequency (HF) and low frequency (LF) spectral components of heart rate variability (HRV) [1]. HF component, [0.15-0.4 Hz], measures the activity of the parasympathetic activity, being synchronous with respiration, and LF component, [0.04-0.15 Hz], is a marker of the sympathetic modulation, at least when measured in normalized units. However, the underlying mechanisms of the VLF component [0.0033-0.04] are controversial. It has been linked with humoral and temperature regulation [2], with slow vasomotor activity or with parasympathetic outflow [3]. These very low frequency components in HRV have also been associated to the modulation observed in periodic breathing [4], which also affects QRS morphology.

QRS slopes have been used to analyze depolarization changes induced by ischemia on the electrocardiogram (ECG), as they are very sensitive to changes in QRS morphology [5]. A VLF modulation has been reported in the upward and downward QRS slopes series of patients with stable angina pectoris [6], synchronous with the VLF component of HRV [7]. Also, a VLF modulation in HRV as well as in ECG-derived respiration (EDR) has been observed in patients with renal failure during hemodialysis [8].

Our hypothesis is that the origin of this VLF modulation is mainly respiration. Results from a previous study using an EDR signal [9] suggest that the VLF modulation observed in HRV and QRS slopes is partially explained by the linear influence of respiration. The main limitation of that study is that an EDR signal rather than the real respiratory signal was used.

In this work we aim to further study the origin of this modulation using the ECG and respiratory flow signals of patients with dilated and ischemic cardiomyopathy. The relation between HRV and QRS slopes in the VLF band is first studied using ordinary coherence to measure the degree of linear relationship. Then, partial coherence is used to find out if linear respiration influence is the main origin of the VLF modulation in QRS slopes series.

## 2. Methods and materials

### 2.1. Study population

The database is composed of 19 patients with dilated cardiomyopathy and 29 patients with ischemic cardiomyopathy. High resolution (1600 Hz) ECGs were recorded and transformed into vectocardiograms (VCGs), which represents the movement of the heart's electric vector in the space using three ortogonal leads: $x(n)$, $y(n)$, $z(n)$. QRS annotation marks were also available. Respiration flow was simultanously recorded at 1600 Hz.

### 2.2. Heart rate variability

QRS marks on the VCG signal were used to extract the HRV signal. A method based on the Integral Pulse Frequency Modulation (IPFM) model, which includes the detection and correction of ectopic beats and misdetections [10], was used to estimate the instantaneous heart rate (HR) signal. The obtained signal was resampled at 4 Hz, obtaining $d_{\text{HR}}(n)$.

### 2.3. QRS slopes

Using the annotation marks on the VCG, the baseline was attenuated via cubic spline interpolation. QRS slopes were measured in a loop-derived lead, $l(n)$, as a previous work showed improved results for this lead over individual standard leads [9]. To compute $l(n)$, the dominant direction $\boldsymbol{u}$ of each QRS complex was determined as:

$$\boldsymbol{u} = [u_{\text{X}}, u_{\text{Y}}, u_{\text{Z}}]^T = [x(n_0), y(n_0), z(n_0)]^T \tag{1}$$

with

$$n_0 = \arg\max_n \left[x^2(n) + y^2(n) + z^2(n)\right] \tag{2}$$

where $n$ spans from 20 ms before to 130 ms after each QRS complex onset. The loop-derived lead was then calculated by projecting the points of the QRS loop onto this $\boldsymbol{u}$ axis [6]:

$$l(n) = \frac{[x(n), y(n), z(n)]^T \, \boldsymbol{u}}{||\boldsymbol{u}||} \tag{3}$$

Finally, $l(n)$ was delineated using a wavelet-based technique [11] to determine the onset and offset of the QRS complex, as well as Q, R and S peak positions. QRS slopes were calculated using the algorithm described in [5], obtaining the slope indices for each beat: $I_{\text{US}}$ and $I_{\text{DS}}$ for the upward and downward slope of the R wave, respectively. $I_{\text{US}}(n)$ and $I_{\text{DS}}(n)$ were obtained by resampling the slope series at 4 Hz.

### 2.4. Ordinary and partial coherence

Ordinary coherence was used to measure the linear relationship between two signals $i$ and $j$ at a given frequency:

$$\gamma_{ij}(f) = \frac{|S_{ij}(f)|}{\sqrt{S_i(f) S_j(f)}} \tag{4}$$

being $S_i(f)$ the power spectral density function of the signal $i$, and $S_{ij}(f)$ the cross-spectrum between signals $i$ and $j$.

When a third signal $k$ is also related to signals $i$ and $j$, partial coherence can be used to measure the relation between $i$ and $j$ after removing the influence of $k$ [12]. Partial coherence was calculated as:

$$\gamma_{ij|k}(f) = \frac{|S_{ij|k}(f)|}{\sqrt{S_{i|k}(f) S_{j|k}(f)}} \tag{5}$$

with

$$S_{ij|k}(f) = S_{ij}(f) - \frac{S_{ik}(f) S_{kj}(f)}{S_k(f)} \tag{6}$$

$$S_{i|k}(f) = S_i(f) - \frac{S_{ik}(f) S_{ki}(f)}{S_k(f)} \tag{7}$$

Power spectral densities, as well as cross-spectra, were determined using the Minimum Variance Distortionless Response (MVDR) [13]. This method was used to achieve higher spectral resolution than the classical periodogram, which is needed in the study of the VLF modulation.

Spectral coherence estimates depend on the parameter of the estimator, and can be higher than zero for uncoupled signals. Thus statistical analysis is necessary to assess whether coherence estimates are significant or not. Statistical analysis is based on the comparison between the actual coherence estimates and a threshold $\rho$ function obtained as the $\nu$-percentile of the coherence between 1000 realizations of couples of white Gaussian noises. In the calculation of the threshold, white Gaussian noises are as long as the actual signals and parameters of the estimator are the also the same.

### 2.5. Segment selection

HRV, QRS slopes and respiratory series were divided into 5-minute segments, where stationarity of the series was assumed. A total of 276 segments were analyzed.

Only those segments for which HRV and QRS slopes presented VLF modulation, that is, they had a peak in the VLF band in the spectrum of $d_{\text{HR}}(n)$ and $I_{\text{US}}(n)$ or $I_{\text{DS}}(n)$ at the same frequency, were considered for further analysis. The spectra were imposed to be "peaky" enough, which means that two conditions are fullfilled: first, at least 50% of the total power in the VLF band is contained in an interval centered around the largest peak $f_o$: [$f_o$-0.01Hz,$f_o$+0.01Hz]; and second, power spectral density values at the interval extremes do not exceed 75% of the value at $f_o$. Besides, ordinary coherence between HRV and QRS slopes was required to be higher than the calculated threshold for a segment to be selected.

Then, we looked for those segments with VLF modulation, not only in HRV and QRS slopes, but also in the respiratory series. Partial coherence was computed in these segments.

## 3. Results

*VLF modulation in HRV and QRS slopes*

The threshold which determines if the coherence value between HRV and QRS slopes is significantly high is 0.65, with an error of 5%. Table 1 shows that 13 patients present the VLF modulation in HRV and $I_{\text{US}}$, 14 patients in the case of $I_{\text{DS}}$. About 50% of the patients which present this modulation had dilated cardiomyopathy, and the rest had ischemic cardiomyopathy (one of these patients was diabetic).

| | $d_{\text{HR}}(n)$–$I_{\text{US}}(n)$ | $d_{\text{HR}}(n)$–$I_{\text{DS}}(n)$ |
|---|---|---|
| # Patients (# Segm.) | 13 (20) | 14 (21) |
| $\gamma_{ij}(f_o)$ | 0.71 $\pm$ 0.06 | 0.72 $\pm$ 0.05 |

Table 1. VLF modulation in HRV and QRS slopes.

*VLF modulation in HRV, QRS slopes and respiration*

Figures 1 shows that some segments clearly present VLF modulation in HRV, QRS slopes and in respiration, denoted as $r(n)$.

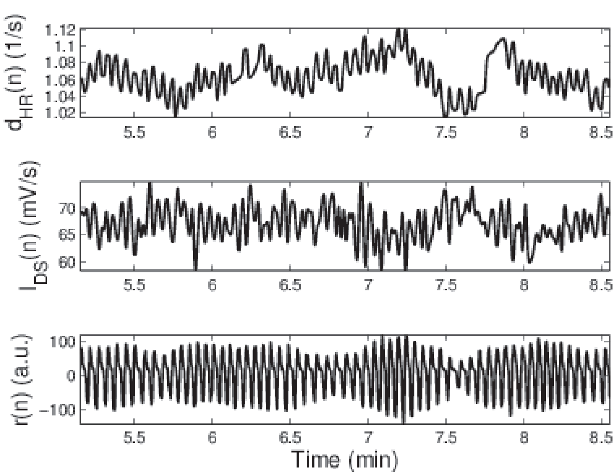


Figure 1. VLF modulation in $d_{\text{HR}}(n)$, $I_{\text{DS}}(n)$ and $r(n)$.

When introducing the respiration signal, some of the segments used in the previous analysis cannot be used, since VLF modulation is not always found in respiration. VLF modulation can be found in HRV, $I_{\text{US}}$ and respiration simultaneously only in 5 patients (7 segments), and in 5 patients (10 segments) in the case of $I_{\text{DS}}$. Table 2 displays the results of partial coherence analysis. Every segment present a lower partial coherence than ordinary coherence, however, only 4 segments have a partial coherence value between HRV and $I_{\text{US}}$ below the threshold, 3 in the case of $I_{\text{DS}}$. Figure 2 shows how the partial coherence drops below the threshold in one of these segments.

| | $d_{\text{HR}}(n)$–$I_{\text{US}}(n)$ | $d_{\text{HR}}(n)$–$I_{\text{DS}}(n)$ |
|---|---|---|
| # Segm. $\gamma_{ij\|k}(f_o) < \rho$ | 4 | 3 |
| # Segm. $\gamma_{ij\|k}(f_o) > \rho$ | 3 | 7 |
| $\gamma_{ij\|k}(f_o)$ vs $\gamma_{ij}(f_o)$ | 0.71 vs 0.75 | 0.73 vs 0.79 |

Table 2. Segments where $\gamma_{ij|k}(f_o) < \gamma_{ij}(f_o)$.

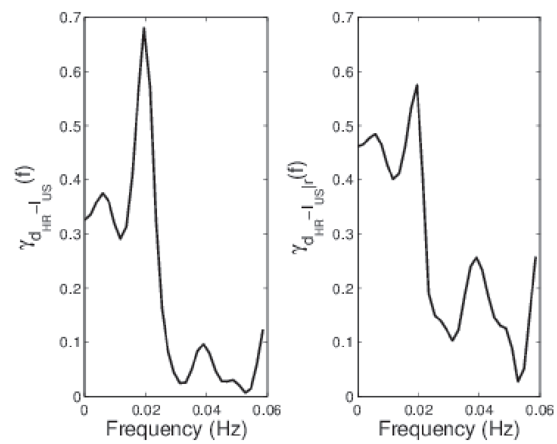


Figure 2. Example of decrease of VLF modulation peak in partial coherence.

## 4. Discussion and conclusion

The hypothesis of this work is that the main source of the linear relation between HRV and QRS slopes in VLF spectral band is respiration. Partial coherence is used to estimate the residual relation between the two signals after having removed the linear influence that respiration exerts on both signals simultaneously. This methodology has already been used to study the influence of respiration over cardiovascular signals [14].

In a previous work [9], an ECG-derived respiratory (EDR) signal was used instead of the real respiration signal, and 64.15% of the segments with VLF modulation in HRV, $I_{\text{US}}$ and EDR presented a drop in the partial coherence below the threshold compared to ordinary coherence, 76% in the case of $I_{DS}$. Note that in this work the percentage of segments whith a partial coherence below the threshold is lower than in [9].

One reason is that the frequency of the modulation does not always coincide perfectly in all three signals. As a result, the coherence peak is not as high as expected, and the coherence threshold has been lowered from 0.7 to 0.65 for this reason. Still, several segments have been rejected even though there was the modulation, but the differences of the frequency caused a very low coherence. In these cases, ordinary and partial coherence is not suitable to measure this relation.

Another reason is that other non-linear mechanisms may cause this modulation, although they can also be related to respiration. Chronic heart failure patients often develop breathing anomalies such as various forms of oscillatory breathing patterns characterized by rises and falls in ventilation, which is called perdiodic breathing (PB). This results in an amplitude modulation, and the spectral peak of this kind of modulation should not be in the VLF band, but around the respiratory peak. These PB events do not always present a VLF component in the respiratory signal, but the amplitud modulation is reflected in HRV and QRS slopes as a VLF modulation. This effect cannot be measured using the coherence analysis.

Using an EDR signal instead of the real respiration, as in [9], more segments present the VLF modulation in all three signals: 10 segments for $I_{US}$ and 12 segments for $I_{DS}$; 6 ($I_{US}$) and 4 ($I_{DS}$) of these segments with a partial coherence value below the threshold. The reason is that the EDR signal used does not follow that amplitude modulation, but instead, it imitates the behaviour of HRV and QRS slopes.

The decrease in partial coherence with respect to ordinary coherence suggests that the origin of the VLF modulation of QRS slopes and HRV can be partially explained by the linear effect of respiration. Still, there may be other effects, such as a non linear relation with respiration in the PB events, which contribute to the genesis of the observed VLF modulation. This phenomenon will be the subject of future studies.

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