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Research Article

QRS Complex Wavelet Analysis Can Distinguish Patients with and without Heart Failure, in the Presence of Left Bundle Branch Block

Kalliopi Papathoma[1*], Anastasios Tsarouchas[2], Dimitrios Mouselimis[2], Eleni Christaina[3], Stavros Chatzimiltiadis[4], Nikolaos Maglaveras[1], Ioanna Chouvarda[1], Efstratios Theofilogiannakos[2] and Vassilios Vassilikos[2]

[1]*Laboratory of Computing, Medical Informatics and Biomedical Imaging Technologies, School of Medicine, Aristotle University, Thessaloniki, Greece*

[2]*Third Department of Cardiology, HIPOKRATIO University Hospital, School of Medicine, Aristotle University, Thessaloniki, Greece*

[3]*Department of Biostatistics, Democritus University of Thrace, Alexandroupolis, Greece*

[4]*First Department of Cardiology, AHEPA University Hospital, School of Medicine, Aristotle University, Thessaloniki, Greece*

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ABSTRACT

Background: Left bundle branch block (LBBB) in heart failure (HF) patients is a negative predictor of survival. This pattern is occasionally recorded in individuals without structural heart disease. The LBBB morphology has not been previously analyzed in a time-frequency domain using wavelet analysis), and thus the factors distinguish LBBB patients from individuals without structural heart disease remain unexplored. The purpose of this analysis was to investigate the variations and the differences in LBBB morphology between healthy individuals with LBBB and patients with HF and LBBB.

Methods: HF patients with LBBB and individuals with LBBB were included in this study. Signal-averaged 90-second Holter monitor recordings were extracted from each subject in orthogonal leads. QRS decomposition in 9 time-frequency bands (TFB) was performed using Complex Morlet wavelets transformation, while the mean and maximum energies of the QRS complexes were calculated for each of the 9 TFBs. The wavelet parameters of HF patients were compared with those of healthy controls.

Results: Wavelet analysis was performed on ECG recordings of 69 HF patients and 17 individuals without cardiac disease. The mean and max wavelet energies of the QRS complex in all TFBs were higher for heart failure patients with LBBB, as compared to healthy individuals with LBBB. Differences were statistically significant in TFB4 and TFB7 (max energy, axis X), TFB4 and TFB7 (max energy, axis Y) and TFB4 and TFB7 (mean energy, axis Y). A multivariate logistic regression model, comprising of the aforementioned wavelet parameters, proved reasonably capable of distinguishing between HF patients and healthy controls with LBBB (AUC=0.854, 80.2% sensitivity and 80.3% specificity).

Conclusion: QRS wavelet analysis revealed differences in the template of the QRS complex between healthy individuals with LBBB and heart failure patients with LBBB. This feature could be used as part of the diagnostic algorithm, a possibility that should be investigated further.

Introduction

Left bundle branch block (LBBB) is reflected on the electrocardiogram (ECG) as a QRS prolongation above 120ms, a delay of intrinsic deflection in leads V5 and V6 of more than 60ms and an absence of Q waves in leads I, V5 and V6 [1]. On the basis of additional insights from computer simulations, the investigators propose stricter criteria for complete LBBB that include a QRS duration ≥140 ms for men and ≥130 ms for women, along with mid-QRS notching or slurring in ≥2 contiguous leads [2]. It is characterized by obstruction of the depolarization's signal through the left ventricle's conduction system. LBBB is usually present in patients with cardiac disease, most

[*]*Correspondence to: Kalliopi Papathoma, Aristotle University of Thessaloniki, School of Medicine, University Campus, 54124, Thessaloniki, Greece; Tel: 00306944502413; E-mail: kpapathom@gmail.com*

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commonly coronary artery disease (CAD) and chronic heart failure (CHF). LBBB occurs in up to 30% of patients with heart failure [3]. In these patients, LBBB is an ominous finding, as its presence correlates with increased mortality and frequency of adverse events [4, 5]. Nonetheless, LBBB is occasionally encountered in healthy individuals, having a prevalence of less than 1% in the general population [6]. Even in these cases, LBBB confers such individuals with a mortality risk of 1.3 [6].

LBBB is associated with poor electromechanical function of the left ventricle, as regional delays in depolarization cause dyssynchronous activation of the ventricular walls. Reduced systolic shortening in regions of the myocardium that depolarize early during systole has been observed as the cause of poorer LV function in the setting of LBBB [7]. Cardiac resynchronization therapy (CRT) is performed by pacing both ventricles and is very effective at ceasing and even undoing the deleterious effects of LBBB on cardiac function and remodeling [8]. In fact, the presence of LBBB predicts which HF patients with reduced ejection fraction stand to benefit the most from CRT therapy [9].

In addition to QRS complex duration and morphology analysis, our group was also subject to a Complex Morlet wavelets analysis ('cmor') of QRS complex, which constitutes a novel technique of orthogonal ECG analysis based on the combination of time-domain and frequency-domain [10]. This technique has been found useful in the detection of small signal components in large ECG waves [10, 11].

Surface ECG provides a time-domain and a frequency-domain analysis of the electrical activation of the heart. However, the frequency content of the signal may provide additional information. The wavelet transform is a mathematical function that has been used for almost three decades as an alternative to the traditional time-domain methods providing a time- frequency domain analysis [12, 13]. Wavelet decomposition of the signal-averaged electrocardiogram has been proposed as a method of detecting small and transient irregularities hidden within the QRS complex with marked accuracy and reproducibility [14, 15].

Wavelet transform (WT) is a widely used method for time frequency transformations and it was adopted by several studies in order to capture the time specific frequency content appearing in the biomedical signals such as ECG [16]. Wavelet analysis of QRS morphologies has been performed in the past, enabling the accurate detection of the Q fiducial point [17, 18]. Also, wavelet QRS analysis has been used for the prediction of response to cardiac resynchronization therapy [19]. At the same time, beat-to-beat wavelet analysis of the P-wave has uncovered significant differences in wavelet properties between healthy controls and patients with paroxysmal atrial fibrillation [20].

The aim of the present study is to delineate the wavelet properties of the QRS complex in HF patients with LBBB and otherwise healthy controls that exhibited LBBB, as well as compare the findings from both groups.

Materials and Methods

I Study Population

The study was designed and executed according to the Declaration of Helsinki. After approval of our institution's Medical Ethics Committee, all participants were provided with a consent form that they agreed to sign. HF patients with LBBB, treated in our Department, have been invited to participate in this study. To avoid heterogeneity, only patients with reduced ejection fraction (HFrEF) included in the study. The control group consists of patients treated by our hospital for non-cardiac causes and exhibited LBBB without organic heart disease. All the patients of the control group underwent a transthoracic echocardiogram and a stress test (stress- echocardiogram or treadmill test). None of them had history of hypertension and diabetes. The diagnosis of LBBB was utilized with the established ECG criteria. QRS duration (QRS>130msec for women and QRS>140msec for men) were used for this study [2]. Patients who were ventricularly paced were excluded from the study.

II ECG Recordings

ECG signals were recorded with a 3-channel digital Holter monitor (Galix Biomedical Instrumentation) for 10 minutes at rest in the X, Y and Z orthogonal leads [21]. The consistent rectangular coordinate system is illustrated in (Figure 1). The sampling frequency was 1000Hz, and the duration of each signal was 90 seconds in order to ensure an adequate and artifact-free signal of the same length for all patients.

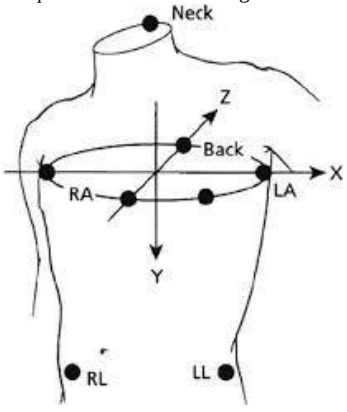

Figure 1: X, Y, Z orthogonal leads.

III ECG Signal Processing and Wavelet Analysis

A signal averaging algorithm was developed to enhance the QRS signal and reduce the noise level prior to wavelet analysis. The first step was the extraction of raw data from three orthogonal leads (X,Y,Z) from the Holter monitor to the computer, followed the signal processing. The signal processing includes; the baseline wander removal which was then achieved through amplitude normalization, baseline correction and application of denoising wavelet filter [22]. Noise was filtered out through application of a de-noising wavelet filter. The linear trend from ECG and the power line interference (50Hz) were removed from every lead. Then a high pass filter and a low pass filter (f1-f2: 0.8Hz-200Hz) was applied. A one-dimensional de-noising function was applied for the wavelet filter. Also, the threshold selection rule is a heuristic variant of the first option using a soft thresholding with a symplet complex wavelet and 5 levels of the wavelet decomposition. Selected the multiplicative threshold for rescaling done using level-dependent estimation of level noise [23].

The following step was included the localization of the R points and the calculation of QRS complexes [24]. All QRS-complexes in each signal were calculated and manually inspected by two blinded in order to exclude the ectopic beats. QRS complexes in every signal were

evaluated, and those found to contain noise or constitute premature ventricular contractions (PVCs) were excluded from the analysis.

Wavelet Analysis and Quantification

Wavelet transformation of the QRS complex was conducted, using the Complex Morlet wavelets analysis [25]. The outcome of a continuous wavelet transform (CWT) is a function of two variables, time and scale. Changing the scaling parameter, results in a function with different frequency content and time spanning. In this respect, each scaled version of the mother wavelet can be mapped to a function with a specific central frequency [20]. The bandwidth and the center frequency were 3 and 1 respectively.

QRS complex was divided into 3 equal parts with respect to time and 3 frequency bands, creating a total of 9 time-frequency bands (TFB). The high frequency range (150-200Hz) is found in bands TFB1, TFB2, and TFB 3; the medium frequency range (100-150Hz) is found in bands TFB4, TFB5, and TFB6; and the low frequency range: (50-150Hz) is found in bands TFB7, TFB8 and, TFB9 (Figure 2). The initial, middle and ending part of the QRS was segmented accordingly. The wavelet features that were calculated were the mean and maximum wavelet energies of the QRS complexes. These were calculated in each of the 9 time-frequency bands for each of the 3 axes, yielding 27 features per recording [26].

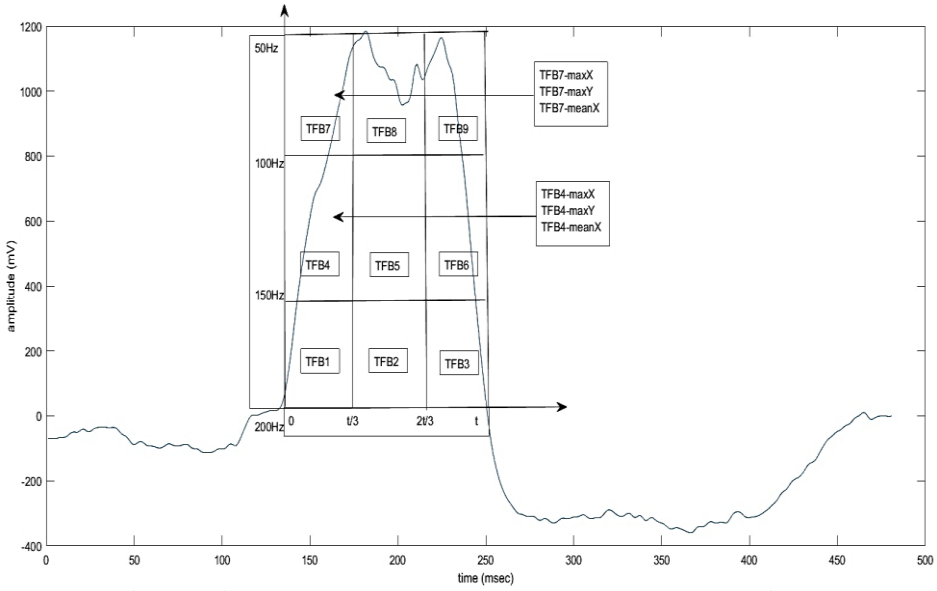

Figure 2: Graphical representation of the time-frequency bands produced during wavelet analysis. TFB Time-frequency band. Also, it is portrayed the 2 statistically significant time-frequency bands (TFB4 and TFB7).

Comparing the Wavelet Properties between HF Patients and the Control Group

The mean and maximum wavelet energies for each time-frequency band were compared between the HF group and the controls. Mean corresponding to the mean energy of QRS complex in a specific time-frequency area and maximum corresponding to the maximum energy of QRS complex in a specific time-frequency area. In order to investigate the ability of QRS wavelet analysis to distinguish between HF patients and healthy controls, a multivariate logistic regression was applied. All wavelet parameters found to be statistically significantly different between the two groups, at a level of $p<0.05$, were included in this model. The following equation describes our model.

$$\log\left[\frac{\text{prob(HF)}}{(1 - \text{prob(HF)})}\right] = \beta TFB4 - MaxX + \beta TFB7 - MaxX + \beta TFB4 - MaxY + \beta TFB7 - MaxY + \beta TFB4 - MeanY + \beta TFB7 - MeanY + \varepsilon$$

The capability of this model to separate HF patients from healthy controls was tested with the ROC curve and AUC analysis. All statistical analyses were performed using IBM SPSS Statistics version 23.0 (Chicago, IL, USA). Mean and range of minimum and maximum values were used to express normally distributed variables, and median and interquartile range for non-normally distributed variables (i.e., all wavelet parameters). Differences between groups were explored with Student's t-test or Mann Whitney U test for normally and abnormally distributed variables, respectively. All p- values were considered significant at the 5% level.

Results

The total population of the study consisted of 86 subjects, 69 HF patients (39 with dilated and 30 with ischemic cardiomyopathy respectively) (Group A) and 17 otherwise healthy individuals with LBBB (Group B). Demographic data of both groups are provided in (Table 1). Wavelet parameters in each of the three orthogonal leads that appeared to differ between HF patients and healthy controls are presented in (Table 2).

Comparing the quantified wavelet properties, maximal wavelet energies of the QRS complex in all frequency bands were higher, on average, for individuals with heart failure, and statistically significant differences

were found in the maximal observed wavelet energy in TFB4 (p=0.004), TFB7 (p=0.013) in axis X; TFB4 (p=0.018) and TFB7 (p=0.008) in axis Y. The mean wavelet energy was significantly increased in HF patients in TFB4 (p=0.038) and TFB7 (p=0.032) (Figure 2).

Figure 3 illustrates the wavelets of a typical HF patient and a healthy individual with LBBB. A multivariate logistic regression has been applied to detect HF by means of wavelet properties (Table 3). The area under the ROC curve was significant (AUC: 0.854; p=0.000; Figure 4, Table 4). This model achieved 80.2% sensitivity and 80.3% specificity in detecting LBBB individuals with heart failure.

Table 1: Demographic characteristics of LBBB patients with and without heart failure.

	Total (SD) N=86	HF (SD) N=69	Control (SD) N=17	p-value
Mean age (years)	66.1 (7.3)	65.7 (8.8)	67.9 (7.3)	0.356
Male gender	66 (76.7%)	54 (78.3%)	12 (70.6%)	0.227
QRS duration (msec)	162.9 (130-196)	166.7 (130-196)	147.5 (130-173)	0.124
Ejection Fraction (%)	31.4 (14.8)	24.8 (5.6)	58.4 (2.7)	0.121

HF stands for Heart failure.

Table 2: Baseline wavelet parameters of LBBB patients with and without heart failure.

	HF (SD) N = 69	Control (SD) N = 17	p-value
TFB4-MaxX	54.36 (82.91)	32.27 (15.47)	**0.004**
TFB7-MaxX	41.96 (77.73)	14.87 (5.09)	**0.013**
TFB4-MaxY	79.32 (101.46)	39.81 (25.05)	**0.018**
TFB7-MaxY	55.60 (85.44)	24.05 (20.26)	**0.008**
TFB4-MeanY	47.24 (69.85)	21.74 (12.35)	**0.038**
TFB7-MeanY	27.37 (43.65)	11.26 (8.61)	**0.032**

HF stands for Heart failure. TFB stands for time-frequency band. Terminology used for wavelet parameters TFB {band} Mean or Max {lead}, e.g., TFB4-MaxY represents the max energy of the QRS complex recorded in TFB 4 in Y lead. Energy is expressed in μV2.P-values in bold indicate significance at 5% or lower.

Table 3: Multivariate logistic regression model.

Variable	B (coefficient of variation)	Odds ratio (95% CI)	p Value
TFB4-MaxX	-0.165	0.848 (0.772-0.931)	**0.001**
TFB7-MaxX	0.282	1.326 (1.123-1.567)	**0.001**
TFB4-MaxY	0.096	1.1 (1.006-1.203)	**0.036**
TFB7-MaxY	-0.143	0.867 (0.771-0.975)	**0.017**
TFB4-MeanY	-0.063	0.939 (0.808-1.092)	0.413
TFB7-MeanY	0.285	1.33 (0.993-1.78)	0.055

TFB stands for time-frequency band. Terminology used for wavelet parameters TFB {band} Mean or Max {lead}, e.g., TFB4-MaxY represents the max energy of the QRS complex recorded in TFB 4 in Y lead. P-values in bold indicate significance at 5% or low.

Table 4: Area Under the Curve.

			Asymptotic 95% Confidence Interval	
Area	Std. Errora	Asymptotic Sig.b	Lower Bound	Upper Bound
0.854	0.045	0.000	0.765	0.943

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

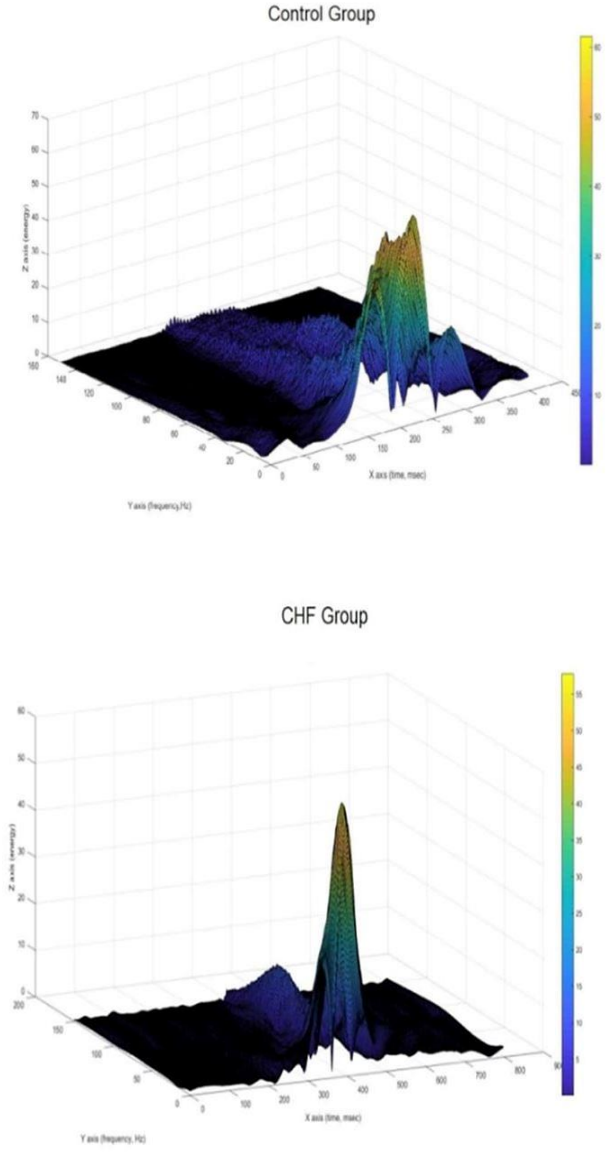

Figure 3: Representative examples of QRS wave wavelet transformation (X axis). On the left is the wavelet representation of a healthy individual with LBBB. On the right, the wavelet representation of a HF patient. Time (QRS wave duration, msec) is shown at X axis, frequency (Hz) at Y axis and QRS wave energy values (μV2) at Z axis.

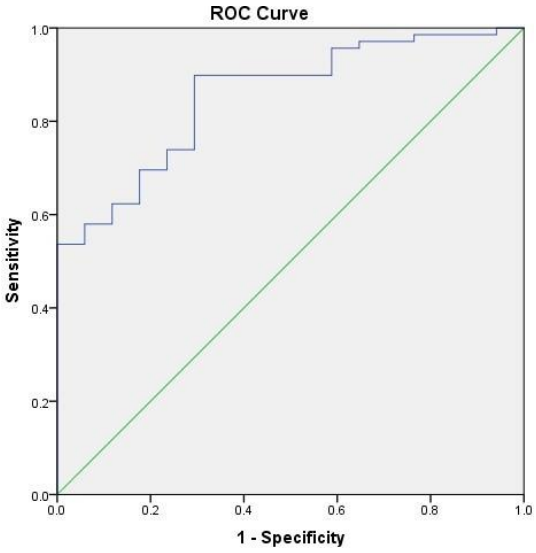

Figure 4: Receiver operating characteristic (ROC) curves: Patients with HF and LBBB vs. healthy people with LBBB for the parameter TFB7-MeanY.

Discussion

The present study was conducted in order to investigate possible differences in the QRS complex in patients with LBBB and HF, compared to healthy controls with LBBB, using a wavelet analysis of the QRS complex.

Our results confirm that there are signal components inside the QRS complex that could distinguish LBBB appearing in individuals without structural heart disease and LBBB in patients with HF and reduced EF. In particular, HF patients exhibited significantly higher maximal wavelet energies than individuals without heart diseases. Four (4) out of the six (6) wavelet parameters incorporated in the multivariate logistic regression model displayed reasonable capacity to distinguish between HF patients and healthy controls. The model was able to detect HF with a sensitivity of 80.2% and a specificity of 80.3% in the sample of the study. It would be interesting to see whether models based on wavelet properties retain their predictive capacity in larger and more heterogeneous sample sizes. It can be observed that with respect to the temporal segmentation, the features from the first part of QRS seem to be more informative than the last part of QRS. The most important features of the model correspond to the low and medium frequency band of QRS. This finding suggests conduction differences, and abnormalities related to delayed or fragmented conduction components, which is a recognizable phenomenon in LBBB, but also and even more so in ischemic hearts.

Some observations can be made about the characteristics of both groups. The mean age (65.7y for the HF group vs 67.9y for the healthy control group) and the male gender (78.3% for the HF group vs 70,6% for the control group) were not significantly differ. QRS duration was also higher in the HF group, but this can be factually attributed to the higher ventricular sizes observed in HFrEF patients, which are tied to an increase in the size of the QRS complex [27].

Conclusion

Our preliminary results indicate that time-frequency analysis of the LBBB-type QRS complex revealed significant differences in HF patients and individuals without heart diseases. The regression model which was created based on these differences achieved reasonable sensitivity and specificity in distinguishing patients with or without heart failure presenting with LBBB. QRS wavelet analysis for diagnostic purposes is still a nascent field, and more research is needed to reliably prove its capacity to distinguish HF patients with LBBB from individuals with LBBB without organic heart disease.

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Conflicts of Interest

None.

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