Predicting Effectiveness of Cardiac Resynchronization Therapy based on QRS Decomposition using the Meyer Orthogonal Wavelet Transformation

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Abstract

Cardiac resynchronization therapy (CRT) has shown clinical benefit for patients with heart failure (HF). However, up to one third of these patients do not respond to CRT. The aim of this study is to determine if specific conduction abnormalities are common to patients who respond to CRT and if these can be identified and quantified on the surface ECG. A signal averaging algorithm was developed to enhance the QRS features and decrease the noise level. Then, a Meyer orthogonal wavelet transformation was applied to the ECG to decompose the QRS.

The receiver operating characteristic curve (ROC) showed that a combination of wavelet coefficients with clinical factors allowed 80% of sensitivity and specificity using the signal from either lead X or Z. Our preliminary results indicate that time-scale decomposition of the high-resolution QRS signal contains information on predicting individuals' response to CRT.

1. Introduction

Heart failure affects nearly 4.9 million people in the USA and is a major cause of morbidity and mortality for all heart diseases. Recently cardiac resynchronization therapy, as a relatively new option for therapy of patients with heart failure, has shown promising results with clinical and functional benefit [1-4]. However, up to 30% of heart failure patients who are selected according to traditional patient selection criteria (QRS > 120 ms, left bundle branch block, New York Heart Association class III-IV, and left ventricular ejection fraction < 35%) do not respond to CRT. Cardiac asynchrony is usually associated with the presence of conduction delay. Consequently, a prolonged QRS duration (> 120ms) on the surface electrocardiogram (ECG) is one of the criteria for CRT patient selection. Yet, recent studies showed that the degree of left ventricular asynchrony did not correlate with the duration of QRS complex and revealed poor prediction of CRT success [5-6]. Therefore, additional markers are needed to identify the patients who benefit the most from CRT. Our objective of this study is to apply time-scale decomposition of the QRS signal to identify QRS contents common to CRT responders based on the Meyer wavelet transformation.

2. Methods

2.1. Study population

This study involved the ECG recordings from patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT). Fifty-seven patients (mean age = 65 ± 11 years, 40 males and 17 females) with left bundle branch block (LBBB) and mid-narrow QRS duration (130-150 ms) were used for this study. The patients responding positively to CRT were defined based on echocardiographic response. A reduction in left ventricular end diastolic volume (LVEDV) superior to 15% between enrollment and 1-year after CRT was considered positive.

2.2. ECG recordings

Standard 12-lead high-resolution Holter ECGs were recorded before implantation using Mortara H12+ (Milwaukee, WI). The first 10 minutes data were recorded while the patients were in supine position. The sampling frequency of the signal is 1000 Hz and the amplitude resolution is 3.75 μV.

2.3. ECG signal averaging

A signal averaging algorithm was developed to enhance the QRS complex features and reduce the noise level. The steps implemented in the signal averaging techniques were:

1) Baseline wander removal: the baseline wander was estimated using linear fitting based on the isoelectric points located within the PR intervals. Then the estimated baseline was subtracted from the original signal.

2) Frank leads: three Frank orthogonal leads were constructed from the 12-lead applying Dowser transform.

3) QRS template: the median beat of 10 correlated (correlation coefficient >= 0.97) consecutive sinus beats was used as QRS template.

4) Beat ranking: all the sinus beats were ranked according to their noise level that was measured using the root mean square (RMS) of the signal inside a window located in the PR segments.

5) Averaging: the beats were orderly entered into the averaging process according to their noise ranking. Only the QRS signals highly correlated with the template (correlation coefficient equal to or higher than 0.97) were selected. Averaging was applied until the noise level of averaged signal reached 0.5μV or no further improvement was obtained with additional beats.

6) The final averaged QRS segment was extracted such as an interval of 512 ms beginning 128 ms before QRS onset.

2.4. Wavelet transformation

Meyer's orthogonal wavelet was constructed in the frequency domain (detail see [7]). The wavelet transform coefficients were computed in the time domain by means of inverse Fourier operation (FT^{-1}) in the following equation:

$$C(a, b) = FT^{-1}\{\sqrt{a}) * S(f) * \Psi_m(f)\}$$

Where C(a, b) is the wavelet coefficient corresponding to scale a and time location b, S(f) is the Fourier transform of the signal and $\Psi_m(f)$ is the Fourier transform of the analyzing wavelet.

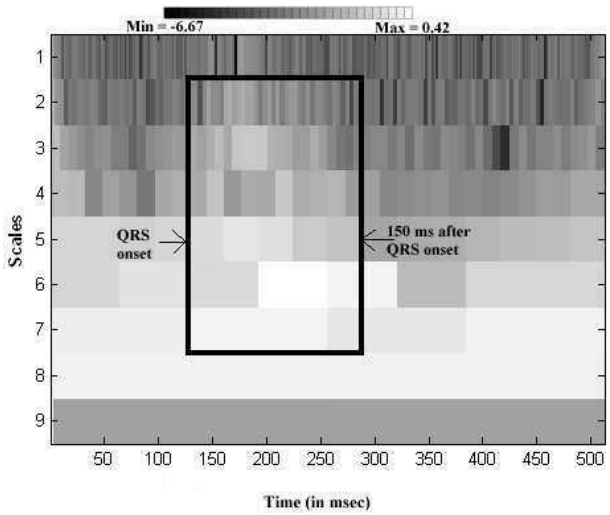

Figure 1. Example of Meyer orthogonal dyadic wavelet decomposition of the 512 ms segment (128 ms before QRS onset and 384 ms after). The outlined rectangle shows the time and frequency area where 70 coefficients were used to analyze QRS. The value of wavelet coefficients in this figure are in log transformed.

The 512 ms segments were decomposed into 512 wavelet coefficients by the Meyer's orthogonal wavelet transform. The wavelet decomposition was applied to the ECG signal from 128 msec before the QRS onset to 384 msec after (Figure 1). The range of QRS duration in our study population varied between 130 and 150 ms. Figure 1 includes the area considered for QRS analysis (70 coefficients). Only the frequency bands corresponding to scale 2 to scale 7 (4-250 Hz) were considered. For easily locating each cell in the time-frequency domain, they were labeled as cellN_M (where N is the scale number and M is the wavelet number for scale N as shown in figure 3).

2.5. Statistical analysis

Univariate analysis was applied to assess the normal distribution of the 70 cells. Stem plot and Shapiro-Wilk normality test were used. A P value < 0.05 was considered significant. If the criteria for normality were not met, the data was log transformed.

One-way nonparametric test was performed on each coefficient from three orthogonal leads to identify the cells significantly different between groups. Logistic regression was applied to find the best model based on the highest likelihood score (chi-square). The predictive scores were computed from the best model and the ROC curves were reported.

3. Results

3.1 Signal averaging

In average across the study population, a noise level of 0.5μV was reached in both lead X and lead Z after averaging around 80 or 60 ranked beats, respectively. The noise level in lead Y could not reach 0.5μV due to more noise (0.8 μV for 90 beats).

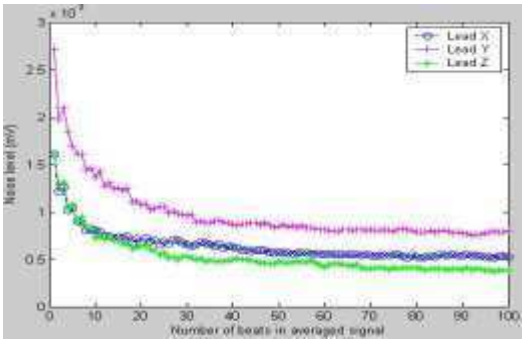

Figure 2. The curves of noise levels (which is the average value over the study population) vs the number of beats in the averaged signal from lead X, Y and Z.

3.2. QRS analysis

Most of the coefficients had a non-normal distribution (with a P-value less than 0.05 in Shapiro-Wilk test). Therefore, logarithm transformation was applied to all coefficients.

After applying nonparametric test, seven coefficients in lead X and six coefficients in lead Z showed significant differences between responders and non-responders. They were cell5_6 cell4_17 cell3_32 cell3_33 cell2_55 cell2_61 cell2_67 and cell2_38 cell2_39 cell2_42 cell2_43 cell2_58 cell2_66, respectively. Only two cells (cell3_30 and cell2_43) in lead Y showed significant differences between responders and non-responders. Figure 3A shows their time and frequency locations.

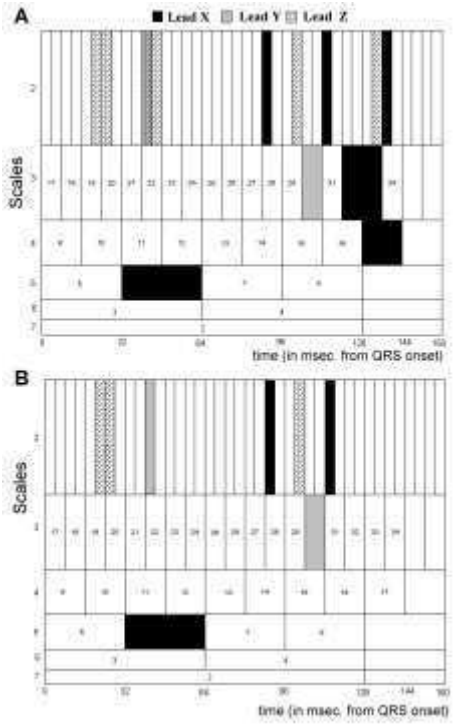

Figure 3. Section of the orthogonal wavelet network used to analyze the QRS (see Figure 1). Shaded areas are the locations of selected cells per lead: A) univariate analysis: cells were significantly different between responder and non-responder. B) multivariate analysis: cells were selected by the best-subset regression analysis.

Three-parameter models (cell5_6 cell2_55 cell2_61 for X and cell2_38 cell2_39 cell2_58 for lead Z) were selected after no significant improvement on chi-square score. The positions of these coefficients are shown in figure 3B. In lead Y, two coefficients (cell3_30 and cell2_43) were selected, but the model was not retained because of lower fitting score. The predictive score for each lead was defined as a linear combination of wavelet coefficients and QRS was forced into the model.

Score_X = -2.17 * cell5_6 + 1.36 * cell2_55 + 1.89 * cell2_61 - 0.04 * QRS + 13.17

Score_Y = -1.3 * cell2_43 + 0.6 * cell3_30 + 0.02 * QRS – 4.7

Score_Z = -1.5 * cell2_38 - 1.57 * cell2_39 + 1.86 * cell2_58 - 0.01 * QRS - 0.05

The ROC curves based on the predictive scores are shown in figure 4. A 73% of sensitivity and a 71% of specificity were obtained from lead X. Similarly, 77% of sensitivity and specificity were obtained from lead Z. A slightly lower sensitivity (64%) and specificity (63%) were obtained from lead Y (not shown).

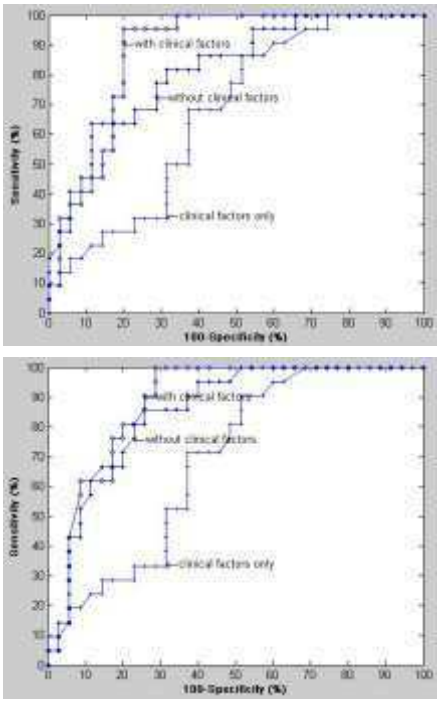

Figure 4. ROC curves generated from logistic regression in lead X (upper) and Lead Z (lower) for the models with and without clinical factor, and the model with clinical factors only.

3.3. Adjusting the model for additional clinical parameters

Recently, Goldenberg et al. [8] identified seven clinical baseline factors associated with echocardiographic response to CRT. These factors are: gender, non-ischemic etiology, left bundle branch block, QRS ≥150 msec, prior

hospitalization for heart failure, left ventricular end diastolic volume (LVEDV) ≥ 125 ml, and left atrial volume LAV < 40 ml. Adding these factors (QRS and LBBB were patients' selection criteria in our population and thus they were not included) into the best-subset regression analysis, only one factor, left atrial volume was selected into the models (interestingly LAV was significant regardless of the selected lead X, Y and Z). There is one coefficient cell2_55 was replaced by cell2_67 in the model combing clinical factors to wavelet coefficients from lead X. The other two models have the same coefficients.

As described in all panels of figure 4, combining clinical parameters with wavelet coefficients increased the classification of the study population with a 81% of sensitivity and a 80% of specificity for the model using lead X, 68% of sensitivity and specificity for the model using lead Y, and 82% sensitivity and 80% specificity from lead Z.

The areas under ROC curve are 0.88 for both lead X and lead Z from our wavelet model with clinical factor, a 30% improvement was observed comparing with the clinical model.

4. Discussions

We hypothesized that heart failure patients benefiting from CRT have specific conduction abnormalities different from the patients that do not respond to such therapy. Using wavelet decomposition and following the methodological concept used for the detection of late potentials, we proposed to use signal averaging QRS technique to identify specific signal patterns associated with CRT benefit. Our results confirm that there are signal components inside the QRS characterizing patients responding to CRT, yet we do not have a clear link between these components and common conduction features (normal or abnormal) that make the use of CRT beneficial.

Our findings reveal that the cells showed significant differences between responders and non-responders in all three leads located around the second fourth and the last fourth of the QRS complex. Most of these cells are in high frequency bands (scale 2-3, 63-250Hz). The logistic regression results showed that the response to CRT is associated with: 1) a reduction in energy of the cells around the second fourth of QRS complex, 2) an increase in energy of the cells around the last fourth of QRS complex. This result may imply a specific delay in the fractionation of the QRS complex, where most energy is delivered at the end of QRS complex. We speculate that this delay might be associated with stronger ventricular asynchrony. Further investigations are required.

LAV was the only clinical factor selected by the best-subset regression analysis. The logistic regression model selected our wavelet coefficients before LAV, this result revealed that our coefficients might provide strong prediction on the benefit of CRT complementing clinical parameters. An independent validation of the model is the next step of this work.

5. Conclusions

In this study, we used an orthogonal wavelet dyadic network for decomposing the QRS signals of cardiac patients enrolled in the MADIT-CRT trial. A signal averaging technique was first applied to enhance the QRS features while wavelets were used to decompose the signal. We identified QRS components characterizing CRT responder prior to therapy.

References

[1] Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-880.

[2] Auricchio A, Stellbrink, C, Sack S, et al. long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002;39:2026-2033.

[3] Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002 Jun 13;346(24):1845-53.

[4] Molhoek SG, Bax JJ, van Erven L, et al. Effectiveness of resynchronization therapy in patients with end-stage heart failure. Am J Cardiol. 2002 Aug 15;90(4):379-83.

[5] Achilli A, Sassara M, Ficili S, Pontillo D, et al. Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and "narrow" QRS.. J Am Coll Cardiol. 2003 Dec 17;42(12):2117-24.

[6] Bleeker GB, Schalij MJ, Molhoek SG, et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. J Cardiovasc Electrophysiol. 2004 May; 15 (5) : 544-9.

[7] Couderc JP, Fischer S, Costello A, et al. Wavelet Analysis of Spatial Dispersion of P-wave Morphology in Patients Converted.from Atrial Fibrilation. Computer in Cardiology 1999;26:699-702.

[8] Goldernberg I, Moss AJ, Hall J, et al. Predictors of Response to Cardiac Resynchronization Therapy in MADIT-CRT. Circulation (In press).

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