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QRS analysis using wavelet transformation for the prediction of response to cardiac resynchronization therapy: A prospective pilot study☆

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Abstract

Background: Wider QRS and left bundle branch block morphology are related to response to cardiac resynchronization therapy (CRT). A novel time-frequency analysis of the QRS complex may provide additional information in predicting response to CRT.

Methods: Signal-averaged electrocardiograms were prospectively recorded, before CRT, in orthogonal leads and QRS decomposition in three frequency bands was performed using the Morlet wavelet transformation.

Results: Thirty eight patients (age 65 ± 10 years, 31 males) were studied. CRT responders (n = 28) had wider baseline QRS compared to non-responders and lower QRS energies in all frequency bands. The combination of QRS duration and mean energy in the high frequency band had the best predicting ability (AUC 0.833, 95%CI 0.705-0.962, p = 0.002) followed by the maximum energy in the high frequency band (AUC 0.811, 95%CI 0.663-0.960, p = 0.004).

Conclusions: Wavelet transformation of the QRS complex is useful in predicting response to CRT.

Keywords: Heart failure; Biventricular pacing; Morlet wavelet transform; QRS complex; Signal processing

Introduction

Cardiac resynchronization therapy (CRT) was introduced as a revolutionary treatment for patients with advanced heart failure and left ventricular (LV) conduction delay, aiming to restore the electrical dyssynchrony, improve LV mechanics and thus reduce heart failure morbidity and mortality.[1–3] Nevertheless, about one third of patients fulfilling the criteria for CRT implantation, as suggested by guidelines,[4,5] show no benefit from this treatment. Patients with wider QRS are more likely to respond possibly because QRS duration correlates with the degree of LV posterolateral wall conduction delay in the presence of left bundle branch block (LBBB).[6] However, QRS duration does not consistently reflect the underlying severity of mechanical dyssynchrony.[7]

Since echocardiographic indices of mechanical dyssynchrony are unreliable and difficult to obtain consistently,[8] the effort to define electrical measures of LV depolarization has become attractive again. Different patterns of LV electrical activation sequence both during intrinsic conduction in LBBB and in response to pacing have been recorded, allowing the conclusion that not all LBBBs are created equally.[6] Surface ECG provides a time-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 two decades as an alternative to the traditional time-domain methods providing a time-frequency domain analysis.[9,10] Wavelet decomposition of the signal-averaged electrocardiogram has been

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proposed as a method of detecting small and transient irregularities hidden within the QRS complex[11] with marked accuracy and reproducibility.[12]

In the current prospective study we tested the hypothesis that wavelet analysis of the QRS complex may predict the response to CRT in patients with heart failure and LBBB who fulfill the classic criteria for CRT implantation.

Methods

Study population

The study complied with the Declaration of Helsinki and was approved by the Medical Ethics Committee of our Institution. All study subjects gave written informed consent for the participation to the study. We enrolled 40 consecutive patients with heart failure referred for CRT to our hospital from September 2009 to March 2011. Inclusion criteria were LBBB (QRS duration >120 ms, QS or rS in V1 and RsR′ in V6) and standard indications for CRT (i.e. EF ≤35%, QRS >120 ms, NYHA III–IV, or NYHA II with QRS >150 ms on optimal medical therapy). Two patients were excluded from final analysis because of unsuccessful implantation of the LV lead and loss of biventricular pacing (<90%) during follow-up, respectively.

Baseline evaluation before CRT implantation consisted of medical history, clinical examination, surface 12-lead ECG, standard echocardiographic study and orthogonal electrocardiographic recordings for wavelet analysis. At six months follow up all patients were reviewed by two study investigators. Clinical assessment and echocardiographic study were performed using exactly the same methodology as at baseline. Regarding the definition of response to CRT a great heterogeneity exists among the published studies. We chose to define response to CRT as the combination of NYHA class improvement by ≥1 and reduction in the left ventricular end-systolic volume (LVESV) by ≥15% as it is more objective and provides a measure of reverse remodeling which is more likely to depend on the electrical activation properties of the myocardial tissue.

Echocardiographic study

All echocardiographic studies were performed at baseline and at 6 months follow-up with the same device (Vivid 7, General Electric, USA) by a single experienced echocardiographer. A study investigator blinded to the clinical data performed the measurements off-line including left ventricular ejection fraction and left ventricular end systolic volume using the Simpson's biplane method from the 4-chamber and 2-chamber apical views.

Orthogonal ECG

Orthogonal ECG recordings were obtained from each patient at baseline before CRT implantation using a 3-channel digital recorder (GBI-3SM, Galix Biomedical Instrumentation, USA) as previously described.[13] The recordings were performed for 3 minutes using a sampling frequency of 1000 samples per second per channel at the very high resolution mode (VHR ECG 0.05–500Hz) with the patient at the supine position in a quiet environment. Seven patches were attached to the anterior and the posterior thoracic wall as indicated by the Holter manufacturer in order to record signals in horizontal (*x* axis), frontal (*y* axis) and sagittal plane (*z* axis) forming an orthogonal lead system (Fig. 1). Five QRS complexes were manually selected (by a study investigator to avoid artifacts) from each subject's ECG and pre-processed with normalization (mean subtraction and division by standard deviation), baseline correction and application of a denoising wavelet filter (wavelet-wiener filtering with biorthogonal mother function).[14]

QRS complex transform

QRS complex transform was performed by a dedicated software built by the Department of Medical Informatics of our Institution using Morlet wavelet analysis (appendix) in three orthogonal leads (*x*, *y*, *z*).[15,16] The beginning and the end of the selected QRS complexes were manually marked in each of the 3 leads (*x*, *y*, *z*). Then the mean and maximum (max) energies of the selected QRS complexes were automatically calculated in each of the 3 leads, in 3 frequency bands [band 1 (high frequency): 200–160 Hz, band 2 (medium frequency): 150–100 Hz, band 3 (low frequency): 90–50 Hz]. In total 18 variables were calculated for every patient (6 in each lead). "Mean" QRS complex amplitude in a given band corresponded to the time-scale (or equivalently spectrotemporal) components of QRS curve in that band, adjusted for the duration of the QRS, whereas the "Maximum (Max)" energy corresponded to the global maximum spectrotemporal energy of the curve of QRS complex in that band. The terminology used to describe the variables was mean{band}{lead} or max

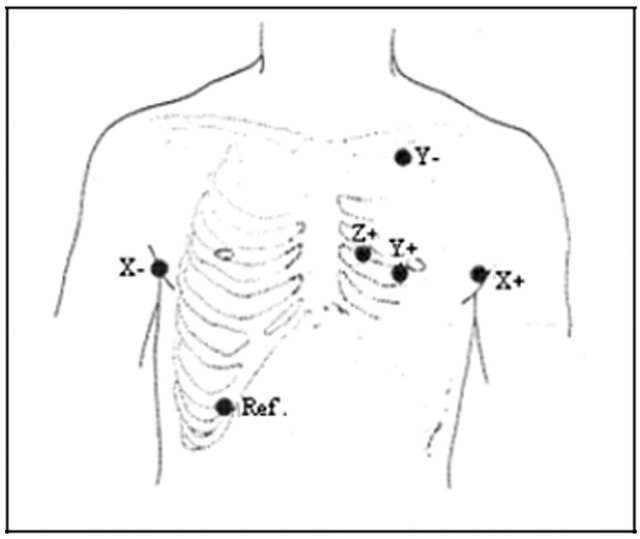

Fig. 1. Orthogonal lead system. Seven electrodes are placed on the chest to record signals in the horizontal plane (*x* axis, electrodes + X and −X in the left and right midaxillary line, fourth intercostals space), frontal plane (*y* axis, electrodes + Y in the standard V3 position and −Y in the superior aspect of the manubrium) and sagittal plane (*z* axis, electrodes + Z in the standard V2 position and −Z immediately posterior to + Z). The seventh electrode (*ref*) is placed in the right hypochondrium. (Of note electrode −Z is not shown in the picture).

{band}{lead}, e.g. mean1x corresponds to the mean energy of the QRS complex recorded in the high frequency band (200–160 Hz) in the x lead.

CRT implantation

CRT implantation was performed as per routine practice by two experienced electrophysiologists and wherever possible a lateral tributary of the cardiac venous system was targeted for the implantation of the LV lead.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (Chicago, IL, USA). Normally distributed variables were expressed as mean and standard deviation, whereas non-normally distributed variables (i.e. all wavelet parameters) were expressed as median and interquartile range. Differences between groups were explored with Student's t-test or Mann–Whitney U test for normally and non-normally distributed variables, respectively. Categorical variables were expressed as absolute number and percentage and were compared between groups using the chi-square test. Variables before and after CRT implantation were compared using Student's paired t-test or Wilcoxon signed ranked test. Univariate logistic regression analysis was performed in order to identify the contribution of each variable in the prediction of response to CRT. Due to the collinearity between wavelet parameters they were entered one by one together with QRS duration (the only clinical variable that was found significant in the univariate analysis) in a stepwise fashion into the multivariate logistic regression model. A predicted probability of response to CRT was obtained from the logistic model and was then assessed using the receiver operator characteristic (ROC) curves. A p value <0.05 was considered statistically significant.

Reproducibility

Wavelet analysis is a semi-automatic method. An operator has to manually select a number of QRS complexes (five in our study) avoiding noise, artifacts and premature beats. Subsequently the operator marks manually the beginning and the end of the QRS complex. The rest of the analysis is done automatically. The same investigator ran the wavelet analysis twice in 10 random patients in order to calculate the intra-observer variability using the following formula: Intra-observer agreement index $= 100-\frac{|x_1-x_2|}{(x_1+x_2)/2}$ in which x_1 and x_2 are the measures obtained in twice repeated evaluations by the same observer using the same method. Two different investigators ran the wavelet analysis in 10 random patients in order to calculate the inter-observer variability using the following formula: Inter-observer agreement index $= 100-\frac{|x_a-x_b|}{(x_a+x_b)/2}$ in which x_a and x_b are the measures obtained by two observers using the same method in the same patient. All wavelet parameters were highly reproducible. The intra-observer agreement index was 99.8–100% and the inter-observer agreement index was 98.5–100%.

Results

Data of 38 patients (mean age 65 ± 10 years, 31 male) were analysed. Baseline characteristics are shown in Table 1. Fifteen patients (39%) had ischemic and 23 (61%) had non-ischemic cardiomyopathy. At baseline mean QRS duration was 165 ± 21 ms (range 120–200 ms) and mean EF was 25 ± 5%. At 6 months follow up NYHA class improved from 3^{2-4} to 2^{1-3} ($p < 0.001$), EF increased from 25 ± 5% to 31 ± 9% ($p = 0.031$) and LVESV decreased from 161 ± 48 ml to 120 ± 42 ml ($p = 0.018$). Twenty-eight patients (74%) were identified as responders to CRT based on LVESV reduction and NYHA class improvement. Baseline QRS duration was higher in responders as compared to non-

Table 1
Demographic, clinical and echocardiographic characteristics of CRT responders versus CRT non-responders.

	Total n = 38	CRT responders n = 28	CRT non-responders n = 10	p Value
Age (years)	65 ± 10	65 ± 10	63 ± 12	0.636
Male gender	31 (82%)	23 (82%)	8 (80%)	0.881
NYHA class, median (range)	3 (2–4)	3 (2–4)	3 (2–3)	0.853
NYHA II (%)	4 (10%)	3 (11%)	1 (10%)	
NYHA III (%)	33 (87%)	24 (85%)	9 (90%)	
NYHA IV (%)	1 (3%)	1 (4%)	0	
QRS duration (ms)	165 ± 21	171 ± 22	142 ± 11	0.005
Left ventricular ejection fraction (%)	25 ± 5%	26 ± 7%	23 ± 5%	0.199
Left ventricular end-systolic volume (ml)	161 ± 48	162 ± 53	158 ± 29	0.887
Ischemic etiology	15 (39%)	12(43%)	3 (30%)	0.526
Atrial fibrillation	5 (13%)	3 (11%)	2 (20%)	0.303
Medication				
β-blockers	34 (95%)	26 (93%)	8 (80%)	0.255
ACEi/ARBs	35 (92%)	26 (93%)	9 (90%)	0.774
Aldosterone antagonists	27 (71%)	20 (71%)	7 (70%)	0.932
Diuretics	33 (87%)	24 (86%)	9 (90%)	0.731
Digoxin	5 (13%)	3 (11%)	2 (20%)	0.456
Amiodarone	9 (24%)	6 (21%)	3 (30%)	0.584

NYHA, New York Heart Association; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

Table 2
Baseline wavelet parameters in CRT responders vs. CRT non-responders.

		CRT responders N = 28	CRT non-responders N = 10	p Value
X	Mean1*x*	24.9 (8.0)	31.0 (9.4)	0.003
	Mean2*x*	45.0 (20.2)	63.0 (30.2)	0.005
	Mean3*x*	198 (234)	420 (408)	0.009
	Max1*x*	25.6 (10.2)	35.5 (9.3)	0.003
	Max2*x*	37.3 (11.6)	54.3 (14.2)	0.005
	Max3*x*	71.6 (37.9)	124.5 (52.1)	0.010
Y	Mean1*y*	25.7 (10.5)	26.7 (14.5)	0.411
	Mean2*y*	51.5 (35.6)	52.7 (56.3)	0.371
	Mean3*y*	277 (338)	213 (264)	0.841
	Max1*y*	28.5 (12.8)	33.2 (18.7)	0.182
	Max2*y*	40.5 (21.1)	49.8 (35.7)	0.112
	Max3*y*	97.8 (48.2)	99.8 (72.4)	0.104
Z	Mean1*z*	22.9 (6.7)	26.1 (9.7)	0.187
	Mean2*z*	40.5 (20.5)	49.9 (31.5)	0.083
	Mean3*z*	180 (127)	226 (220)	0.141
	Max1*z*	22.2 (13.4)	41.0 (16.2)	0.040
	Max2*z*	34.2 (13.4)	41.0 (16.2)	0.062
	Max3*z*	77.5 (45.3)	102 (65)	0.072

Terminology used for wavelet parameters: mean or max{band}{lead}, e.g. mean 1*x* represents the mean energy of the QRS complex recorded in the high frequency band (200–160 Hz) in the *x* lead, mean 2*x* the mean amplitude of the QRS recorded in the medium frequency band (150–100 Hz) in the *x* lead and mean 3*x* the mean amplitude of the QRS recorded in the low frequency band (90–50 Hz) at the *x* lead. Energy is expressed in μV^2.

responders (171 ± 22 ms versus 142 ± 11 ms, p = 0.005). Baseline echocardiographic and clinical characteristics were similar between responders and non-responders.

Wavelet parameters in each of three orthogonal leads in responders and non-responders are presented in Table 2. In both groups the biggest proportion of the QRS energy was distributed in the low frequency band (90–50 Hz) while a small amount of energy was recorded in the medium and high frequency bands. Wavelet parameters of the QRS complex in all frequency bands in *x* lead were lower in responders as opposed to non-responders. Representative Fig. 2 shows these concepts. No significant differences were noted in the y lead. In the z lead mean QRS energies were similar among groups but maximum energy in the high frequency band was higher in non-responders.

Predictors of response to CRT

Univariate analysis (Table 3) showed that baseline QRS duration and wavelet parameters representing all frequency components of the signal recorded in the *x* lead (mean1*x*, mean2*x*, mean3*x*, max1*x*, max2*x*, max3*x*) could predict response to CRT. QRS duration was a positive predictor of response while all wavelet parameters were negative predictors of response. Other clinical parameters (age,

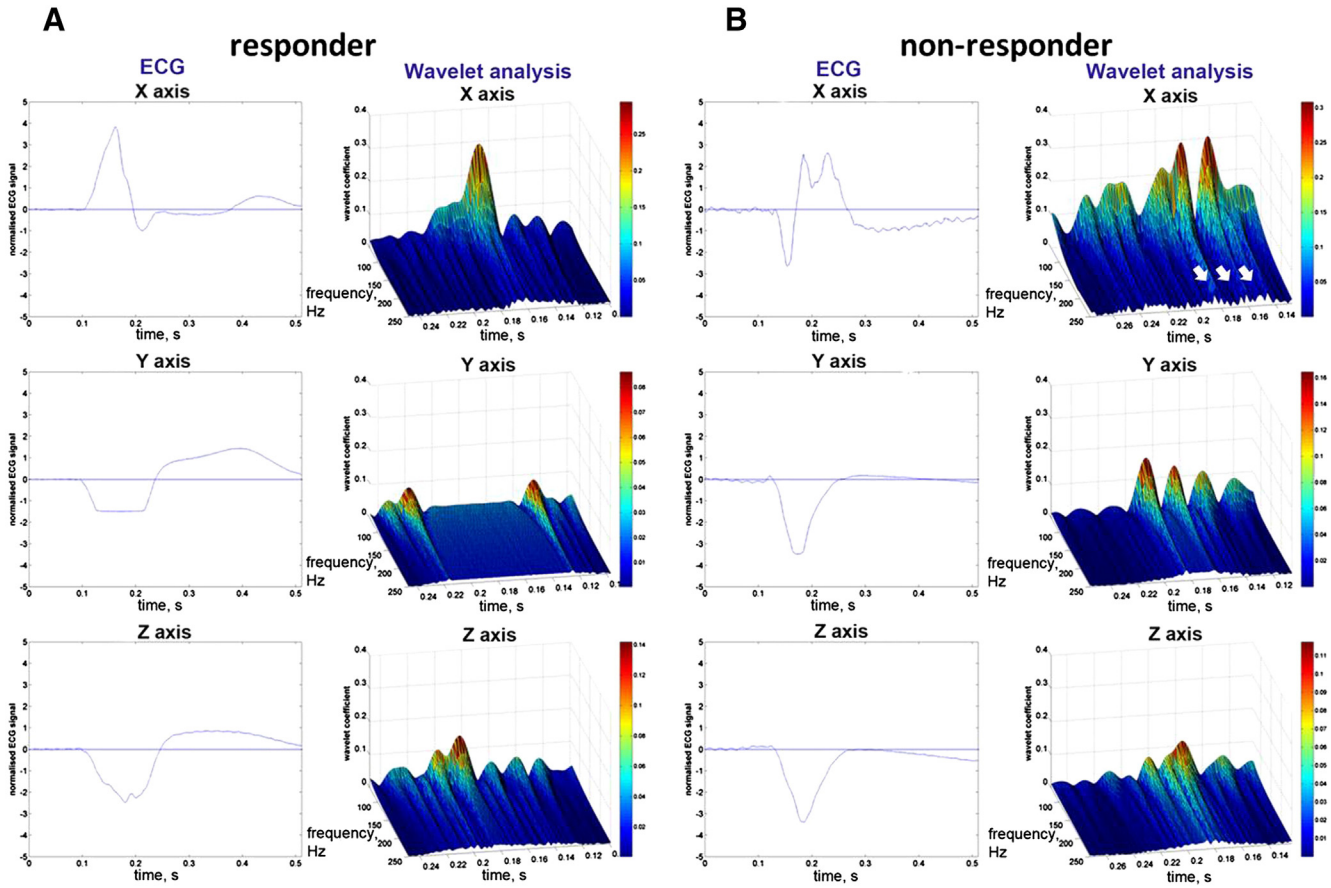

Fig. 2. ECG of left bundle branch block QRS and the corresponding wavelet analysis in leads *x*, *y* and *z* in A) CRT responder and B) CRT non-responder. Note that in panel B (non-responder) more high frequency components are observed (indicated with arrows) in *x* axis in comparison to panel A (responder). Color illustration online.

Table 3
Univariate logistic regression analysis (only significant results shown).

	Univariate logistic regression		
	B (coefficient of variation)	Odds ratio (95% CI)	p Value
QRS duration	0.052	1.05 (1.01-1.10)	0.022
Mean1*x*	−0.165	0.85 (0.74-0.97)	0.020
Mean2*x*	−0.030	0.97 (0.94-1.00)	0.082
Mean3*x*	−0.003	1.00 (0.99-1.00)	0.061
Max1*x*	−0.151	0.86 (0.76-0.97)	0.017
Max2*x*	−0.076	0.93 (0.87-0.99)	0.028
Max3*x*	−0.025	0.97 (0.95-1.00)	0.025

NYHA, New York Heart Association; LV, left ventricular.

gender, heart failure etiology, baseline EF and NYHA class) were not significantly related to response in our population (Data available by contact with the authors).

Multivariate logistic regression was applied to investigate whether any of the wavelet parameters were related to response independently of QRS duration (Table 4). This analysis revealed that mean1*x* which represents the mean energy recorded in the high frequency band in *x* lead can predict response independently of QRS duration. Moreover max1*x* which represents the maximum energy recorded in the high frequency band in *x* lead was the only significant predictor of response to CRT when it was assessed together with QRS duration.

The ROC curves depicting the sensitivity and specificity of QRS duration, max1*x* and the combination of QRS duration and mean1*x* are presented in Fig. 3. QRS duration alone had good predicting ability but worse that the wavelet parameters (AUC 0.782, 95%CI 0.627–0.934, p = 0.009). Second best predicting variable was max1*x*, i.e. the maximum energy in the high frequency band in *x* lead (AUC 0.811, 95%CI 0.663–0.960, p = 0.004) and the best predicting ability of response to CRT was shown with the combination of QRS duration and mean1*x*, i.e. the mean energy in the high frequency band in *x* lead (AUC 0.833, 95%CI 0.705–0.962, p = 0.002).

Wavelet analysis in ischemic versus non-ischemic cardiomyopathy

No significant differences were observed between patients with heart failure of ischemic and non-ischemic etiology (Data available by contact with the authors). Patients with non-ischemic cardiomyopathy showed a trend to have shorter QRS duration on surface ECG (160 ± 22 ms vs. 173 ± 19 ms, p = 0.063). Response to CRT was similar between the two groups according to heart failure etiology and all wavelet parameters were similar.

Table 4
Multivariate logistic regression models.

		B (coefficient of variation)	Odds ratio (95% CI)	p Value
1st model	QRS duration	0.038	1.04 (0.93-1.09)	0.039
	Mean1*x*	−0.141	0.87 (0.75-1.01)	0.048
2nd model	QRS duration	0.031	1.03 (0.98-1.08)	0.195
	Max1*x*	−0.151	0.86 (0.76-0.97)	0.017

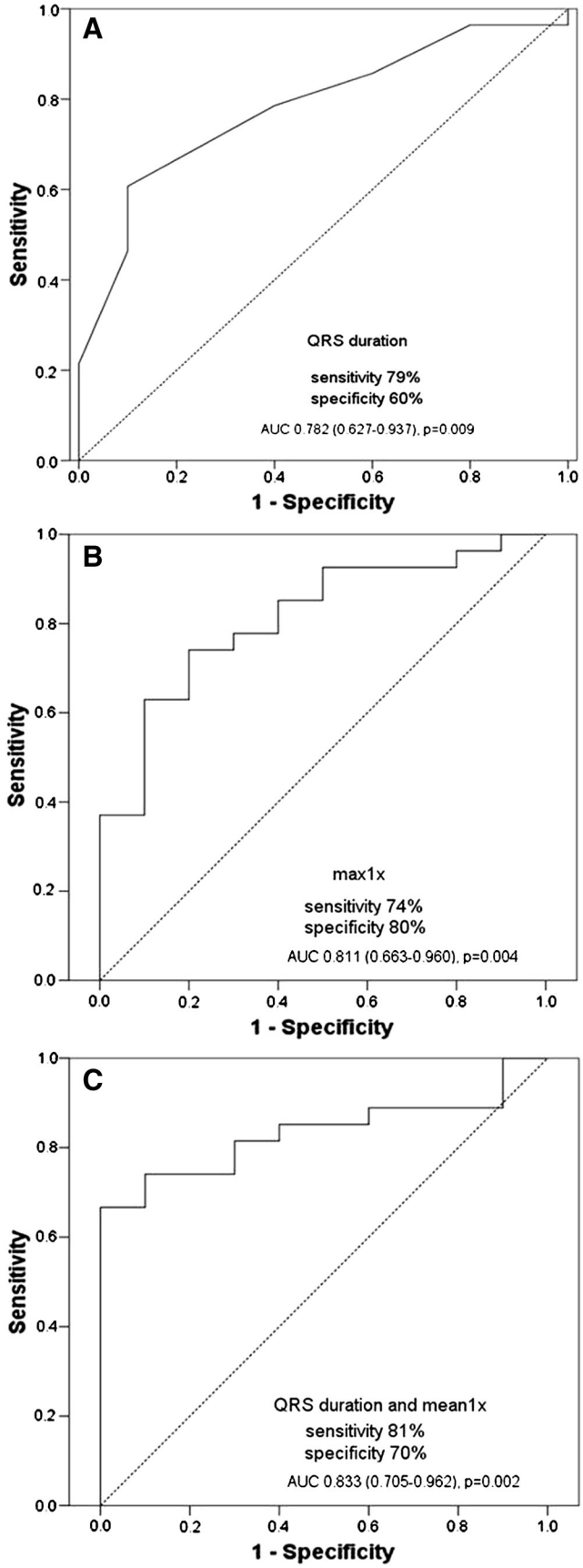

Fig. 3. Receiver operating characteristic curves depicting the sensitivity and specificity of A) QRS duration, B) max1*x* (maximum energy recorded in the high frequency band in the *x* lead) and C) the combination of mean1*x* and QRS duration for the prediction of response to cardiac resynchronisation therapy.

Discussion

In this prospective pilot study we applied QRS decomposition using the Morlet wavelet transformation before cardiac resynchronization therapy and showed that there are significant differences between patients who respond to CRT as compared to those who do not. More specifically, our study showed for the first time that a) In *x* lead mean and max QRS energies in responders were lower as compared to non-responders, b) In *z* lead maximum QRS energy was lower in responders as compared to the non-responders in the high frequency band and c) In multivariate analysis the mean QRS energy in the high frequency band in *x* lead (mean1*x*) along with the QRS duration and the maximum QRS energy in the high frequency band in *x* lead (max1*x*) were found to be independent predictors of response to CRT.

Morlet analysis of QRS predicts CRT responders

We found that the frequency components of the electrical activation signal differs between responders and non responders to CRT and bigger components localised in the higher frequency bands are associated to non-response to CRT. Previous studies have emphasized that the patient-specific electrophysiologic substrate can strongly influence the efficacy of CRT.[17] Langner et al first reported that notching of the QRS in the surface ECG in patients with coronary artery disease may represent high frequency components of the electrical signal.[18] Similar observations were also made by other investigators, all concluding that high frequency components of the ECG are associated with a myocardial pathology, such as fibrosis or ischemia.[19,20] Cardiac magnetic resonance studies validated that fragmentation of the QRS complexes on ECG is associated with intraventricular systolic dyssynchrony and subendocardial fibrosis in patients with non ischemic dilated cardiomyopathy.[21] Our findings suggest that patients with LBBB who present higher QRS energies in high frequency bands are less likely to respond to CRT, suggesting that abnormal myocardial substrate in this group may jeopardize the efficacy of biventricular pacing. However, it is unclear whether max1*x* and mean1*x* in combination with QRS duration predict non-response independently of measures of scar burden, such as delayed enhancement magnetic resonance imaging or ECG Selvester score and this could be addressed in a future study. Previously, the Morlet wavelet transformation of the QRS complex revealed increased power and number of peaks in the high frequency range (150–250 Hz) in patients with intraventricular conduction abnormalities and prior myocardial infarction, which may reflect the transformation of the excitation front passing through infarct lesions.[22] Moreover, patients with dilated cardiomyopathy who progressed to heart failure had higher maximum count and higher surface area in the wavelet analysis and this may reflect a higher degree of interstitial fibrosis.[11] A recent study used wavelet analysis of the QRS complex with the Morlet function to show that high-frequency hidden powers within the QRS complex could contribute to the prediction of lethal arrhythmias post myocardial infarction.[23]

Of note, mainly wavelet parameters in the *x* axis had predictive value. A possible explanation for this finding is that activation abnormalities in lead *x* represent the delay between the septal to lateral left ventricular activation. Cardiac resynchronization therapy shortens the septal to lateral wall delay and consequently improves the left ventricular function. Severe substrate abnormalities may possibly cause a non-reversible left ventricular abnormal activation in lead *x*. Electrical activation in leads y and z is less affected by cardiac resynchronization therapy. However, this is only an assumption which is not possible to prove with the currently available analysis.

Morlet wavelet analysis versus QRS duration

Another important finding of the present study is that max1*x* derived from the wavelet transformation of the QRS complex is better predictor of response to CRT than QRS duration and the combination of mean1*x* and QRS duration is better than QRS duration alone. We may hypothesize that wavelet analysis is superior to the surface QRS duration for identifying small irregularities within the QRS complex, and temporal spread of activation-related components, which in turn may be associated with poor response to cardiac resynchronization therapy.

QRS analysis using the Morlet wavelet transformation may be used as a quick, safe and cheap screening tool before CRT implantation should larger scale studies validate our findings and indicate reproducible cut off values. This may be particularly useful among patients with “borderline” indication for CRT or with debatable characteristics such as non LBBB intraventricular conduction delay.

Study limitations

The small study population does not allow for the calculation of robust cut-off values for the wavelet parameters that would be able to predict response to CRT. However, this is a proof of concept pilot study which provides consistent data indicating that larger studies are warranted to validate our findings. In our study the CRT response rate was higher than average similar studies probably due to a) high percentage of baseline characteristics that favour a positive response to CRT, such non-ischemic cardiomyopathy, wider QRS and left bundle branch morphology and b) exclusion of patients with <90% biventricular pacing in follow up. Delayed enhancement magnetic resonance imaging of the myocardium to define areas of fibrosis was not available thus depriving this study from additional evidence regarding the relationship between high frequency components of QRS energy and myocardial substrate. Also dyssychrony was not assessed before implantation and we do not know whether mean1*x* or max1*x* correlate to the septal to lateral LV activation delay. Due to the small sample size and the design of this pilot study the multivariate analysis was limited to the wavelet parameters and the QRS duration. Other variables that have been shown to affect the response to CRT, such as heart failure etiology, gender, etc, were not added to the model as our aim was to

investigate whether there is any additional information regarding the prediction of response within the time-frequency components of the QRS. Last, patients with non-LBBB morphology were not included because the initial aim of the present study was to explore differences in the QRS complex within patients with LBBB morphology in the surface ECG. However, the population of patients with non-LBBB morphology wide QRS that are treated with CRT is of great interest to be studied using wavelet analysis.

Conclusions

Wavelet analysis of the QRS complex may provide a quick and non-expensive tool, additional to the QRS duration of the surface ECG, for the identification of patients who are more likely to respond to CRT. The presence of high frequency components within the QRS complex may be predictive of non-response to CRT. Further confirmation of this hypothesis should be done in large scale clinical studies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jelectrocard.2013.08.003.

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