Predictive Analysis of Cardiac Resynchronization Therapy Response by means of the ECG

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Abstract

Aims: *Cardiac Resynchronization Therapy (CRT) is an effective treatment for heart failure patients with moderate to severe symptoms. Unfortunately, a significant proportion of patients (up to 35%) do not respond to CRT (patients called "non-responders"). This results in a large cost-effectiveness relation for heart failure treatment. This study aims to assess the prediction response to CRT by means of analysing the ECG.*

Methods: *We retrospectively analysed the surface ECG and QRS previous to CRT implantation in 45 consecutive patients with dilated (27) or ischemic (18) cardiomyopathy. We extracted the QRS and then processed a measure of energy of a discrete version of the Stockwell Transform. This feature was used to discern non-responder patients to CRT.*

Results: *10 out of 45 patients were clinically judged as non-responders to CRT. We observed that, on average, non-responders presented significant lower values for this energy measure than patients who responded favorably to the therapy (with median values 95538 vs. 48516 for responders and non-responders, p-value $<$ 0.05). Using energy in the spectrum as feature to predict patients' response, as well as mean duration of QRS complexes, our obtained performances for a linear least-squares classifier were: accuracy (77.78%), sensitivity (80%), specificity (70%).*

Conclusion: *The current study presents a novel approach to obtain early predictions of potential candidates to CRT in patients suffering from heart failure by means of calculating the energy of the ECG, which may open a door to reduce and try to minimize the number of CRT treatments with unsuccessful results.*

1. Introduction

Heart failure is a condition generally generated by low contraction capacity of ventricles. However, some patients with heart failure do not only present poor contraction, but also ventricles are desynchronized. This deteriorates, even more, performance of cardiac function.

Cardiac resynchronization therapy (CRT) is a well-accepted therapy for patients with heart failure (HF), left ventricular (LV) systolic dysfunction, and QRS prolongation. Biventricular pacing is associated with an improved quality of life, increased functional capacity, reduction in hospitalization for heart failure, and increased survival[1, 2]. Unfortunately, a significant proportion of patients (up to 30-35%) do not respond to CRT therapy ("non-responders") adversely affecting the utility and cost-effectiveness of this form of device therapy for HF[3].

There are many suggested reasons for an inadequate response to CRT such as absence of dyssynchrony previous to the implant of the device, persistence of LV dyssynchrony after CRT, phrenic nerve stimulation, lead dislodgement, or suboptimal programming of device.

Recently, guidelines have made an effort to define the profile of patients to implant a CRT device in order to increase the response to this therapy and to reduce the numbers of non-responders. Indication of CRT relies on the morphology and duration of QRS. The indication with a higher level of evidence is for patients with a left bundle branch block and a QRS width above 130 to 150 ms. CRT is also recommended for patients with right bundle branch block and a QRS width above 150 ms. Nevertheless, there is still a need to improve the selection of patients to optimize the response to CRT.

The present retrospective study introduces a new measure in order to improve the prediction results of response to CRT. This measure is related with the energy of QRS complexes of patients with heart failure before CRT im-

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plantation, as it is detailed in the subsequent sections.

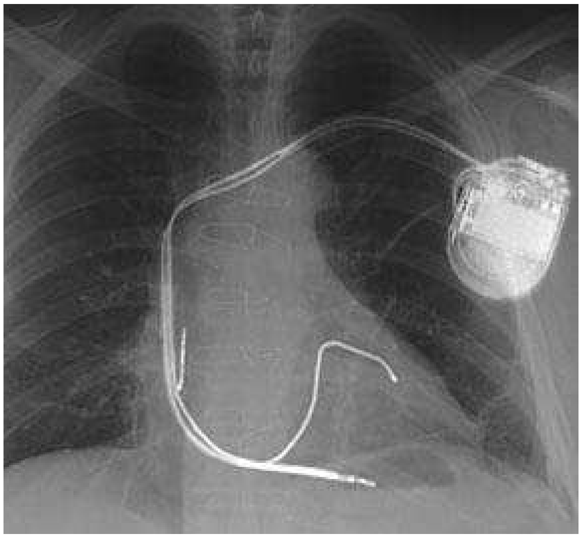

Figure 1. X-ray of patient undergoing CRT by pacemaker stimulating both ventricles (right and left).

2. Materials

45 patients with heart failure who were undergone CRT and who were optimal candidates to be responders to CRT conformed the population of this retrospective study. Surface ECG was acquired in a tertiary center (Hospital Universitari i Politècnic La Fe, Valencia). Duration of ECG segments was 5 seconds, which is a common duration for 6×2 printout displays [4].

Patients had dilated (27) or ischemic (18) cardiomyopathy. An increase in left ventricular ejection fraction (LVEF) of 5% or more was used in this study as an objective measure of cardiac structural improvement. Thus, patients were considered as responders when left ventricular ejection fraction (LVEF) increased by $\geq$5% and New York Heart Association class by $\geq$1 after three months of CRT implantation. According to these guidelines, 35 out of 45 patients were clinically judged as responders to CRT.

Details about population of the dataset are included in Table 1.

3. Methods

3.1. Signal Preprocessing

Baseline and powerline interference were first removed from the surface ECG signals. In particular, baseline wander was reduced by means of cubic splines [5]. Then, we proceeded to delineate the ECG in order to detect onset and endset of QRS complexes.

Table 1. Distribution of patients who conformed the retrospective study.

	Responders	Non-responders
All patients	35	10
Dilated cardiomyopathy	24	3
Ischemic cardiomyopathy	11	7

3.2. Measure of energy

Time-frequency transforms overcome the drawback of providing information about how varies spectral content along time, which cannot be addressed by Fourier analysis. This way, time-frequency analysis is optimum for non-stationary signals (as the ECG), which have time-dependent properties.

There are several time-frequency transforms, with different properties. The main drawback of most of them is how they deal with the uncertainty principle, which states that it is not possible to provide good time and frequency resolution simultaneously once the size of the time window is fixed. One of the most popular transforms which provides globally referenced phase and progressive resolution (i.e. good frequency resolution at low frequencies and good time resolution at high frequencies) is the Stockwell Transform. Progressive resolution is obtained by a frequency-adaptative size of window, as it is detailed in its analytical expression [6, 7]:

$$(Sf)(\tau,\nu) = |\nu| \int_{-\infty}^{\infty} g_0(\nu(t-\tau)) e^{-2\pi i \nu t} f(t)\, dt, \quad (1)$$

where g_0 denotes a Gaussian window. It can be seen as a STFT where the window length varies depending on the frequency. However, the main disadvantage of this transform is related to its very high computational cost and memory requirements. Fortunately, an efficient fast and non-redundant implementation based on a dyadic scheme was described in 2010 [8], which is known as General Fourier-family Transform (GFT).

In the present study we have used the efficient implementation (GFT) in order to estimate a measure of the energy of the QRS complexes. Thus, we have defined this measure as E:

$$E = \sum_{\omega=2}^{\omega=B} \frac{\sum_{t=0}^{t=N-1} |GFT(t,\omega)|^2}{\omega_c^2} \quad (2)$$

where GFT are the coefficients of the efficient implementation of the Stockwell Transform for each QRS complex, B is the number of frequency bands of the time-frequency space, w_c denotes the central frequency of each frequency band, and N is the number of time windows for each frequency band. E has been obtained by dividing by w_c^2 according to [9] (Proposition 3.4, with parameters $\alpha = 2, \beta = 1$).

The final feature used to predict response is the average of the energy measurements for all QRS complex for each patient: $(\sum_{k=1}^{k=n} E_k)/n$, where n denotes the number of QRS complexes for each ECG signal.

4. Results

As above-said, our dataset consisted of 45 electrocardiograms of patients suffering heart failure who were optimal candidates to CRT response. In order to obtain an estimation of the response, we found a linear separator by means of solving the least-squares problem.

Performances obtained were global accuracy (i.e. proportion of correctly classified patients), sensitivity and specificity (proportion of responders and non-responders correctly classified, respectively according to clinical data):

$$ACC = \frac{TP + TN}{TP + FP + TN + FN} \quad (3)$$

$$Sensitivity = \frac{TP}{TP + FN} \quad (4)$$

$$Specificity = \frac{TN}{TN + FP} \quad (5)$$

where TP (true positives) was the number of responders who were classified as responders, TN (true negatives) was the number of non-responders who were classified as non-responders, FP and FN were the non-responders and responders who were erroneously estimated as responder or non-responders, respectively.

Table 2 depicts the features of the cohort of patients under study, whereas Table 3 shows performances after applying linear least-squares fitting. Results are also detailed for those patients with dilated or ischemic cardiomyopathy. In addition, Figure 2 depicts the Region of Convergence curve for the classification results.

It can be observed that non-responders present significantly lower values of the proposed energy measurement than responders. Indeed, the subgroup of patients with ischemic cardiomyopathy is the one that presents better performances (Table 3) with significant differences (Table 2). Those patients who presented dilated cardiomyopathy were the ones who presented lower specificity results. However, these results should be carefully considered due to the small number of non-responder patients included in this subgroup (only 3). More analysis and enlarged datasets would be necessary in order to provide a complete analysis.

Table 2. Mean features: measure of energy (Eq. 2 and QRS duration for the cohort of patients under study before CRT implantation. * denotes statistical significance: p-value <0.05 for Wilcoxon test.

	Measure of energy QRS	QRS duration (ms)
Responders	95538*	225
Dilated cardiomyopathy	73927	228*
Ischemic cardiomyopathy	76130*	222
Non-responders	48516*	180
Dilated cardiomyopathy	40256	148*
Ischemic cardiomyopathy	31768*	194

Table 3. Classification results for the dataset once linear least-squares fitting has been applied.

	Accuracy	Sensitivity	Specificity
All patients	77.78%	80%	70%
Dilated cardiomyopathy	77.78%	79.17%	66.67%
Ischemic cardiomyopathy	77.78%	81.82%	71.43%

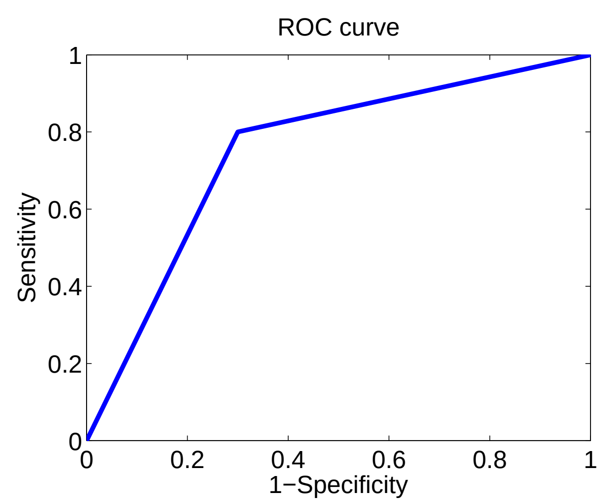

Figure 2. ROC curve for the linear least-squares classifier. Area Under the ROC curve is 0.75

5. Conclusions

In this paper we have presented a retrospective study that points to an energy measurement of QRS as a complementary feature to QRS duration in order to predict response to CRT in those patients with heart failure. Results have shown that this feature is significantly smaller for non-responders to CRT, and it is also significantly smaller for patients who had ischemic cardiomyopathy. Future work will focus on improving results and enlarge the dataset.

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