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Morphological Analysis of T-wave in Vectorcardiographic Leads System by a Bi-Gaussian Approach in Patients under Effect of Salbutamol

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Abstract— **There are several models of decomposition of the electrocardiogram (ECG). Some of these models are intended to describe the ECG signal, and others are more specific to extract the relevant information relating to individual waveform which contributes to explain the P-QRS complex. The latter approach may be particularly suitable for a portion where a morphological analysis of the ECG is of particular interest, as the cardiac repolarization segment or T-wave. This study aims: to model and detect useful patterns in the evaluation of T wave morphology, which explains the different changes in ventricular repolarization during inhalation of Salbutamol.**

I. INTRODUCTION

The normal mechanical operation of the mammalian heart depends on the electrical operation, reflected in the sequential activation of specialized pacemaker cells in the heart. The T-wave of the ECG is attributed specifically to the ventricular repolarization by the generation of action potentials in three ventricular cardiac cells: endocardial cells, M-cells and epicardial cells [1].

Many cardiac pathologies manifest themselves at the cellular and molecular level. Understanding and extrapolation to the clinical variables, such as electrocardiogram (ECG) and vectorcardiogram (VCG) would be an invaluable aid for diagnosis and treatment of patients [2]. The VCG is a 2D record by three pairs of bipolar leads perpendicular to each other (orthogonal leads).

Remarkable progress has been made in defining the membrane phenomena that cause the cellular action potential in cardiac cells. The relation among the sequence of cardiac excitation along the whole heart and the clinical variable such as ECG or VCG is reasonable detailed. However, there has been relatively little progress in explaining the T-wave of the electrocardiogram [3]. The assessment of ventricular repolarization has focused on the estimate by measuring the QT interval duration. There is currently great interest in studying ventricular repolarization, due to the fact that, pathologically, a long QT interval is related to the onset of a cardiac event. The European Society of Cardiology and the Food and Drug Administration (FDA) have recommended measuring the QT interval during the evaluation of new drugs [3], [4].

Although, some researchers still considered the QT interval as a gold standard, the measured QT interval is hampered due to there is no consensus about a proper methodology or an algorithm defined on measuring the starting and ending points of the QT interval. In fact, the evaluation of the end of the QT interval is not a straightforward task, particularly for hypoglycaemic ECG morphologies [4], [5], [6].

Salbutamol (INN) or albuterol (USAN) is a short-acting β_2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease [7].

Episodes of hypoglycaemia and drugs as salbutamol in adults and children induce abnormalities in cardiac repolarization [8], [10] which is also modulated by autonomic neuropathy [9]. Therefore, it is necessary more sophisticated analysis of T wave morphology to reliably detect the onset of hypoglycaemia. This article presents the methodology and the results of a pilot study to carry out morphological analysis of the T-wave through the bi-gaussian function in diabetic patients with established neuropathy, sub-clinical neuropathy and no neuropathy under effect of inhaled salbutamol.

II. MATERIAL AND METHODS

The set of data used in this study was the vectorcardiographic lead system (X, Y, Z) of seventeen diabetic patients with all ethical requirements. The patients were classified according to the following conditions: five with established neuropathy, seven with sub-clinical neuropathy and five without neuropathy. All the measurements were taken at 5 different time steps for each patient: at basal situation before the inhalation of salbutamol and four specific intervals of measurements 10, 20, 40 and 60 minutes after application. The whole methodology was developed using MATLAB R2010b software. The VCG was based on the Frank VCG-lead system, ECG signals were averaged over 5 minutes (around 100 beats); resample at 1000Hz; filtered to reduce noise and artefacts; and orthogonalized to eliminate the error produced by the non-perpendicular placement between the electrodes.

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A. *Principal Component Analysis (PCA)*

The detection of the complex P-QRS and T-Wave at the VCG is carried out by wavelet transform, given by the first derivative of Gaussian function. However, the three leads of the VCG were correlated through a statistical technique as the PCA, while not throwing overboard the variability present in the data set [11], [12].

Principal component analysis (PCA) is a data analysis technique with various uses including dimensionality reduction, quality control, extraction of interpretable derived variables, and outlier detection [11]. In this view, the X lead and Y lead were more sensitive to represent the changes during the different situations studied.

$$A = U\Sigma V^T \tag{1}$$

where A is a lead of VCG, U is a column-orthonormal N × r matrix, r is the rank of the matrix A, Σ is a diagonal r × r matrix of the eigenvalues λi of A, and V is a column-orthonormal M × r matrix [11], [12].

B. *Repolarization Integral (RI)*

The repolarization integral function RI (t) of the T-wave is defined as follows:

$$RI(t) = T_{amp}(t)dt \tag{2}$$

where t= 0 is by definition the J point and $T_{amp}(t)$ is the amplitude of the T wave at the time *t* after the J point [13].

RI is constructed and fitted to a sigmoid distribution using the Hill equation as shown in Fig. 1:

$$RI(t) = V_{max} * \left(\frac{t^n}{K_m^n + t^n}\right) \tag{3}$$

The Hill equation represents the cumulative distribution function of the T-wave, and its derivate allows fitting the T-wave with a bi-gaussian function as shown in Fig. 2. The Hill equation is well known from enzyme kinetics and electrophysiology [13], [14]. The three constants used in this equation are (see Fig. 1):

- V_{max}(mV*s) corresponds to the total T-wave area.
- K_m(s) is the time when 50% of the T-wave area is reached.
- n (dimensionless) is related to the maximum slope of the RI, corresponding to the "s shapeness" of the RI.

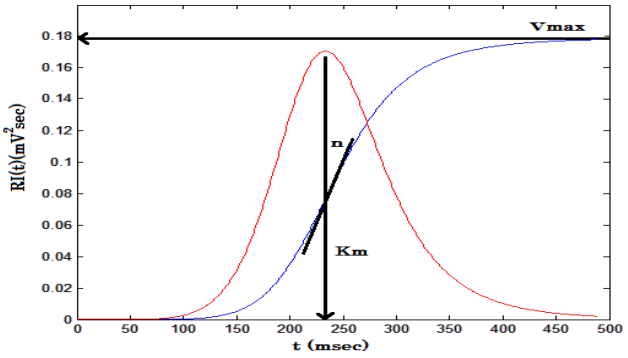

Figure 1. Schematic example of a T wave (*red*), its corresponding repolarization integral (*blue,*) and the three Hill parameters (*black*).

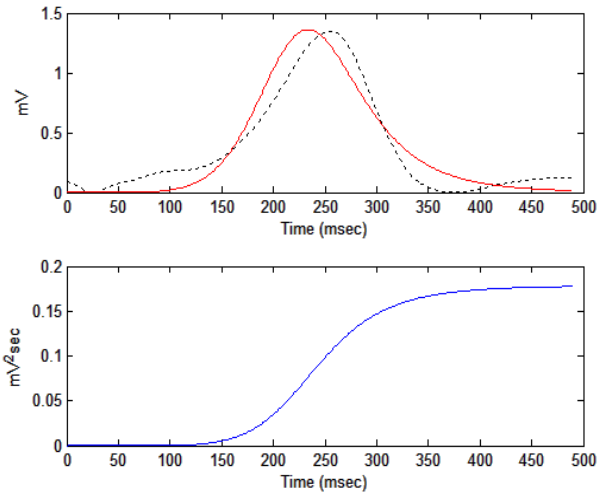

Figure 2. Example of T wave (*upper panel*) and its repolarization integral. *Dotted black line* indicates original data; *solid red line* indicates reconstructed T-wave derived from the Hill equation, *solid blue line* indicates the Hill equation fitting.

C. *Bi-Gaussian Model*

After getting the repolarization integral (RI) through the Hill equation fitting, it was calculated the derivative of the repolarization integral of each curve to get the reconstructed T-waves. Then, the parameters that describe these new curves were calculated.

The morphology of these curves is similar to the bi-Gaussian function (Fig. 3). Therefore, it was performed a mathematical analysis of the parameters needed to model this curve [4], [15].

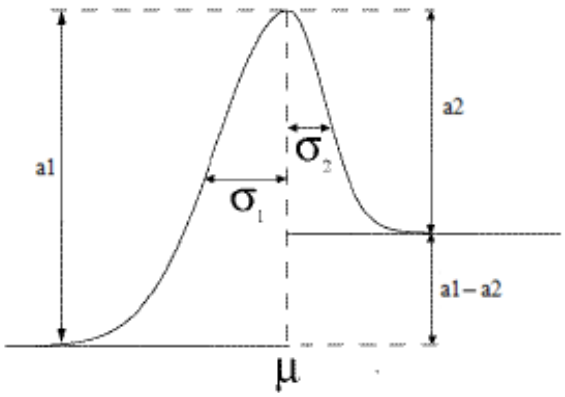

Figure 3. Bi-gaussian function (BGF) with $a_1 \geq a_2$[4]

The bi-gaussian function (BGF) is a five-parameter function made of two half-Gaussian functions in this case with the same mean but with two different amplitudes.

For a given T-wave, the five parameters of the bi-gaussian model produced are the following outputs: "a1" as the T-wave amplitude for the first-half Gaussian measured at Tpeak (mV), "a2" as the T-wave amplitude for the second-half gaussian (mV), σ1 is the "early-T" fitting the ascending phase of the T-wave and σ2 is the "late-T" describing the descending phase of the T wave, and μ is the time when Tpeak is reached [4], [15].

The five parameters are related mathematically as follow:

when $a_1 \geq a_2$:

$$f(x,\mu,\sigma_1,a_1) = a_1 * \exp\left[-0.5\left(\frac{x-\mu}{\sigma_1}\right)^2\right] \qquad x \leq \mu \tag{4}$$

$$f(x,\mu,\sigma_2,a_2) = \left\{a_2 * \exp\left[-0.5\left(\frac{x-\mu}{\sigma_2}\right)^2\right] + (a_1 - a_2)\right\} \qquad x > \mu$$

when $a_1 > a_2$:

$$f(x,\mu,\sigma_2,a_2) = a_2 * \exp\left[-0.5\left(\frac{x-\mu}{\sigma_2}\right)^2\right] \qquad x > \mu \tag{5}$$

$$f(x,\mu,\sigma_1,a_1) = \left\{a_1 * \exp\left[-0.5\left(\frac{x-\mu}{\sigma_1}\right)^2\right] + (a_2 - a_1)\right\} \qquad x \leq \mu$$

The value of the parameters a_1 and a_2 are very important for an optimal graphic and analytical representation of the model, for this reason, it considered the two situations when one of these is bigger or equal than the other one.

The indices of skewness and kurtosis were measured because these are descriptors of the shape of a probability distribution. The skewness was measured because the second-half Gaussian has an elongation greater than twice the mean. Also, the kurtosis was also measured to know how narrow or broad are the signals among themselves.

III. RESULTS

The results show basically as through the Hill equation, you get a perfect reconstruction of T-waves as shown at the Fig. 4 and Fig. 5.

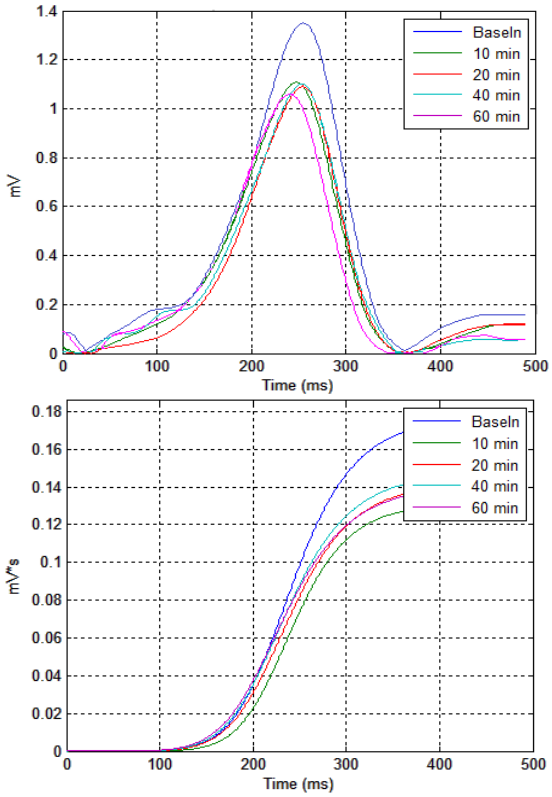

Figure 4. T-waves original (*upper panel*). Hill equation fitting (*lower panel*) in X lead.

It should be noted as due to this method is possible to find functions and mathematical models that are consistent and it may throw parameters for the quantification of the different situations.

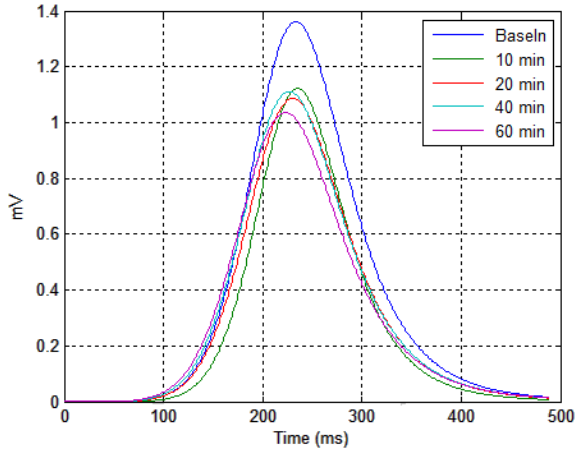

Figure 5. Reconstructed T-waves in X lead at different time steps.

The methodology was applied to all the subjects in this study at the five situations, obtaining a satisfactory fit and obtaining parameters that can be useful to assess repolarization. For the statistical analysis was used the Univariate ANOVA with post hoc test of Bonferroni, and the results are shown in Table I and Fig. 6.

TABLE I
STATISTICAL ANALYSIS OF SKEWNESS (X LEAD) ON FIVE DIFFERENT TIME STEPS

Time steps	**No Neuropathy (5 subjects)**	**Sub-clinical Neuropathy (7 subjects)**	**Established Neuropathy (5 subjects)**
Baseline	1.50 ± 0.24	1.53 ± 0.27	1.52 ± 0.27
10 minutes	1.54 ± 0.18	1.45 ± 0.28	1.35 ± 0.30
20 minutes	1.63 ± 0.21	1.32 ± 0.28	1.32 ± 0.35
40 minutes	1.57 ± 0.14	1.29 ± 0.26	1.36 ± 0.29
60 minutes	1.58 ± 0.20	1.47 ± 0.30	1.26 ± 0.28
Total	**1.57 ± 0.19**	**1.41 ± 0.28**	**1.36 ± 0.29**

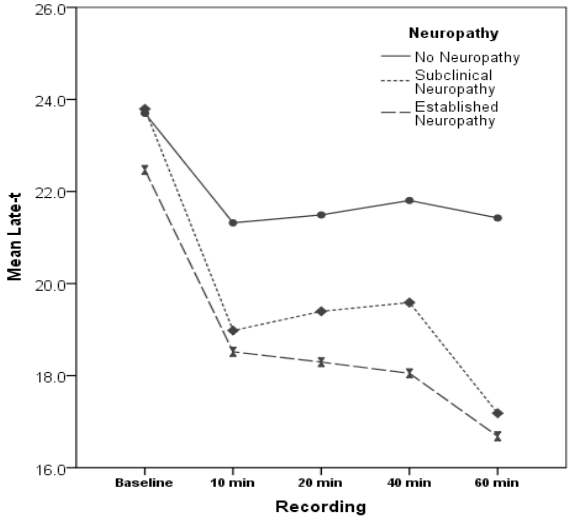

Figure 6. Mean late-T values of σ_2 on the five situations for the seventeen subjects in X lead.

The descriptive statistics analysis shows that the test of between subject effects of the dependent variable skewness was significantly different with (p=0.020) among the groups, no neuropathy is significantly different of established neuropathy (p=0.024) and no neuropathy is almost significantly different of sub-clinical neuropathy (p=0.087), where (p=0.05) is considered significantly different.

At the 10 minutes situation was performed an one-way ANOVA with post hoc tests of Bonferroni for the dependent variable μ (time when Tpeak is reached) and the results are shown in Table II and Fig. 7.

TABLE II
STATISTICAL ANALYSIS OF THE MEAN μ (X LEAD) ON 10 MINUTES SITUATION

Time step	No Neuropathy (5 subjects)	Sub-clinical Neuropathy (7 subjects)	Established Neuropathy (5 subjects)
10 minutes	188.4 ± 23.4	150.6 ± 16.7	166.6 ± 20.9

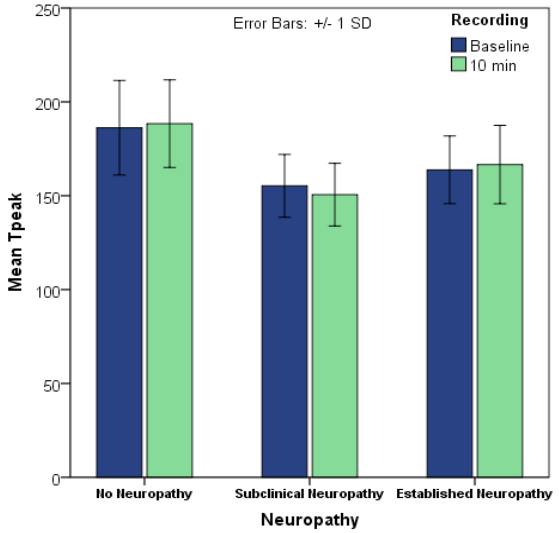

Figure 7. Mean±SD values of μ for the baseline situation and 10 minutes after inhaled salbutamol situation in X lead.

The statistics analysis for the parameter μ show that the test of between subject effects was significantly different with (p=0.020) among the groups and no neuropathy is significantly different of established neuropathy (p=0.018), where (p=0.05) is considered significantly different.

For this pilot study with 17 subjects using this approach it was possible to show the difference between the parameters studied on effects for inhaling salbutamol on the morphology of the T-wave in subjects with no neuropathy; sub-clinical neuropathy and established neuropathy.

IV. Discussion

The skewness for the X lead showed an almost significant reduction for the sub-clinical group (Table I) and the parameter μ at the transition between baseline situation and the 10 minute after application of salbutamol showed a decrement for the sub-clinical neuropathy group that help distinguish among the three conditions of neuropathy as shown in Fig. 6. On the other hand, the σ2 (late-T) showed an interesting behaviour for the three groups that can be useful for distinguishing clear and separately the subjects of the different groups, but for future analysis of the methodology a larger number of subjects is needed.

This methodology gives a good and objective interpretation about the different changes in the morphology of the T-wave under effect of a drug such as salbutamol, and it could be useful for testing other drugs with so far unknown effects on cardiac repolarization.

Using mathematical models to represent and help differentiate objectively the changes in the morphology of a physiological signal, such as the T-wave, this avoid subjective evaluations that currently happen with the QT interval assessment associated with hypoglycaemia, however more research is needed to verify or reject this approach.

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