Development of a Software Tool for the Estimation of the Autonomic Nervous System Performance by Heart Rate Variability, QT Segment Variability and QT Dispersion

Desarrollo de una Herramienta Software para la Estimación del Desempeño del Sistema Nervioso Autónomo usando Variabilidad del Ritmo Cardiaco, Variabilidad del Segmento QT y Dispersión QT

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ABSTRACT

The evaluation of the Autonomic Nervous System (ANS) status can be performed by the measurement of the cardiac frequency variability, the variability of the QT segment and the dispersion of the QT segment. This paper presents the implementation of these estimations by means of Wavelet Transform-based algorithms and the Yule-Walker's spectral estimation. Electrocardiographic records 20 minutes long were evaluated, having 15 minutes taken in a

continuous way. Parameters of cardiac fluctuation were taken out from a population of 92 patients, who presented first stroke and carried out with a strict inclusion protocol to evaluate their cardiac frequency variability. Statistical tests were performed to determine the repeatability of the measurements.

KEYWORDS: Stroke, Autonomous Nervous System, Cardiac Frequency Variability, Spectrum, Vagal-Sympathetic Balance.

RESUMEN

La evaluación del estado del sistema nervioso autónomo (SNA) se puede realizar mediante la medición de la variabilidad de la frecuencia cardiaca, la variabilidad del segmento QT y la dispersión del segmento QT. En este trabajo se presenta la implementación de estas estimaciones mediante algoritmos basados en la transformadaWavelet y la estimación espectral de Yule-Walker. Registros electrocardiográficos de 20 minutos de duración fueron evaluados, con 15 minutos tomados de forma continua. Parámetros de la fluctuación cardiaca fueron tomados de una población de 92 pacientes, quienes presentaron el primer accidente cerebrovascular y llevaron a cabo un protocolo de inclusión estricto para evaluar su variabilidad en la frecuencia cardiaca. Las pruebas estadísticas se realizaron para determinar la repetibilidad de las mediciones.

PALABRAS CLAVE: Accidente cerebrovascular, Sistema Nervioso Autónomo, Variabilidad de la Frecuencia Cardìaca, Espectro, Equilibrio simpático-vagal.

1. INTRODUCTION

Signal processing gives mathematic tools that are appropriate for the analysis of fluctuations in cardiovascular physiological processes. This allows the evaluation of the integrity and performance of these systems, guiding the therapeutics to be used in a given patient and facilitating the prognosis [1].

The present study pretends, through the measurement of the Heart Rate Variability (HRV), to know in a separated way the influence of each subsystem constituting the autonomous nervous system (ANS), i.e. the sympathetic and the parasympathetic system, over the total variations of the cardiac frequency. Particularizing the behavior of each sub-system allows the quantification of the balance between excitatory responses (sympathetic) and inhibitory answers (para-sympathetic), typical of the mentioned system [2] [3].

By definition, the HRV is classically based on the measurement of the variations between heartbeats starting from the detection of RR peaks of the electrocardiogram, these calculations overlook the origin of these fluctuations, variations that can be influenced by the changes in the wide QT complexes and by damages on ANS fibers that innervate the cardiac muscle [4] .

This research aims to reduce the level of uncertainty in the measurement of HRV, by considering the variations originated by changes in duration of QT segments [5] and damage on ANS fibers over the cardiac muscle [6] . When considering them before doing measurements, one could expect to draw refined information of the cardiac physiology, clearing up the punctual source of the HRV, and in this way serving as a tool to determine the morbidity of patients with damage on the ANS [7].

The quantification of the measures described before is performed by an algorithm that detects characteristic points from the beginning of the QRS complex and from the final of the T wave [8]. In this way, we calculate the variability of the QT interval (VQTI) and the dispersion of the interval (QTd) in 5, 10 or 15 minutes of ECG signals, and determine the level and heterogeneity of the electrocardiographic trace over the heart surface. A software was developed, FISIGMESH, under Matlab® environment, which has the tools for building a signal of HRV and variations of the QT segment (Tachogram) using the protocol provided by Sainte Beuve et al. [9] to calculate the dispersion of the QT segment.

The developed software has the necessary tools allowing the physiologist to interpret the electrocardiographic trace, to distinguish and modify the heartbeats that don't have originated at the sinoatrial node (ectopic heartbeats) [10], which are not product of the variations determined by the ANS.

The paper exposes initially a database of cardiac signals and medical data of stroke patients, as a base for the

design of the software. It describes important concepts for the proper interpretation of the physiological measurement of the ANS and shows how the parameters were calculated to define the balance of the system. In the same way, the paper identifies the necessary considerations so that an ectopic heartbeat doesn't modify the calculation of the HRV measurements.

2. DISPLAY OF CARDIAC SIGNALS FOR SOFTWARE VALIDATION

For the validation of the designed software, electrocardiographic signals taken with a Biopac MP35 system were used. The system has three independent channels of acquisition, which were used to take the derivations DI, DII, and the precordial V2.

The ECG signals were taken with a sampling rate of 500 Hz, for 15 continuous minutes and 5 minutes of the precordials V1-V6 [11]. These signals are stored together with medical information from the patient and the Cerebral Tomography of each one of them.

The database of electrocardiographic signals belongs to a stroke study that was conducted at *Hospital Universitario de Santander (Colombia)*, which counts with 145 registers in total. 92 registers belong to patients with first stroke, and among them, 37 registers were selected to evaluate the designed software. More information about this database can be found in the work of Niño [11].

3. MEASUREMENT OF THE AUTONOMOUS CONTROL OF THE CARDIAC SYSTEM

The regulation of the different body functions in the organism is mediated by mainly two systems: one conscient (Somatic Nervous System) and another one unconscious (Autonomous Nervous System – ANS). Regarding the ANS, it is made up by two fundamental branches: the sympathetic (which accelerates) and the parasympathetic (which slows down). These components are synergic and deal with an essential equilibrium for life in the organisms [12] [3].

The heart, which is innervated by autonomous fibers, regulates itself autonomously by means of the sympathetic and parasympathetic systems. These two systems interact mainly in the sinoatrial node, rising the permissiveness to the passage of electrical stimuli or reducing it, respectively, which in turn accelerates or slows down the cardiac frequency.

To evaluate the ANS status, different physiological tests are performed, such as the tilt table test or temperature changes tests. These tests cause alterations in the organism, executing physiological reflexes that lead into a change of the cardiac frequency.

The present study develops various calculations that are needed for estimating the HRV and to determine the variations of the QT segment (VFQT). They will allow to involve in the analysis of the cardiac frequency also the variations due to the repolarization of the heart (T wave), and in this way verify how much the measure of the HRV is influenced by the VFQT.

A tool to calculate the dispersion of the QT segment was developed, as explained on the C section. This measurement allows the evaluation of the triggering of the cardiac pulse.

The technique that was implemented in this research makes use of the Wavelet's transform (WT) of the Spline family of second degree, useful to determinate maximum and minimum points of a wave, according to Martínez et al [8]. In previous jobs like the Olarte and Sierra [13] it is recommended the use of this family in particular.

A. QRS Detection

Figure 1 shows the cardiac signal in time together with its spectral components. The principal components are shown on the band of frequency of 1 Hz and 40 Hz.

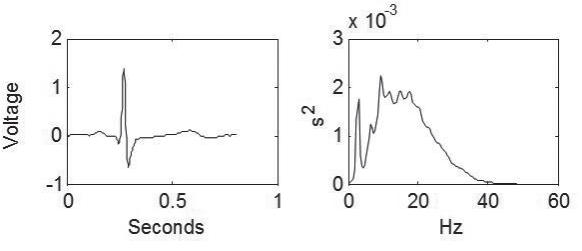

Figure 1. *Time profile (left) and Spectral Components of the Cardiac Signal (right).*

For a sampling rate of 500 Hz, the QRS complex spans between 30 samples and 55 samples, while the R wave lasts less than 35 samples. Taking these aspects into account, the Mallat's algorithm could get until the fourth level of decomposition [14].

The central axis of the determination of the R waves is the correct threshold of wave distinction specification. Martinez et al [8] suggest that this threshold is associated to the RMS value of the signal on every level of decomposition.

Taking the voltages of the signal over these thresholds, the maximum and minimum modules lines are determined, being the cross at cero the mark that signals a point of inflection in the original cardiac signal. This localization is valid at the different levels of Wavelet decomposition, selected to depurate the localization of the QRS complex.

For the detection of the maximum points of the QRS complex, we consider that the heartbeats are not too close to each other. Having two very close complexes, one of them wouldn't be physiological because of it would be eliminated by redundancy of an R peak.

In the process described before, it can't be determined which heartbeat does not belong to the normal cycle of the electric beat of the heart. These beats are called ectopic for not having as origin the sinoatrial node. The variations of the cardiac frequency due to the ectopic heartbeats have to be analyzed to determine in which way these should impact over the considerations of the HRV calculations.

B. QT interval detection

The final detection of the T wave requires of special considerations for its proper definition. Páez and Salgar [15] suggest the usage of the Wavelet's transform with spline family of second order for the determination of the beginning of the QRS and the ending of the T wave. In Martínez et al [8] it is shown that the principal components of the T wave are found on the frequency ranges of 4 Hz to 8 Hz, being the reason of which the multi-resolution analysis reaches the fourth level for the detection of this wave [8].

The Q wave has frequencies between 25-30 Hz, for its detection the signal is decomposed until the level two using the WT spline of second order [8].

Once the QRS complex is detected, a window is taken 12 samples (96 ms) to the left of the R peak in the second level of the WT. At this level, the detection of the Q peak is performed taking it from the closest cross to zero to the R peak.

Figures 2a and 2c show graphically the localization of the mentioned event –for the beginning of the QRS-. The green points belong to the Wavelet's transform of the signal, the original signal is presented in black and the red points show the crossing at zero of the WT, that indicates a maximum of the original signal.

To determine the point where the QRS complex ends (defined as J point), the level two of the WT is used, as shown in Fig 2b and 2d. At this level, a window of about 15 samples (120 ms) is taken at the right of the R point. The inflection points of the transform are analyzed to find out the location of the J point, corresponding to the second maximum (the red dot as it is shown on Fig 2b and 2d).

From the detected J point, a new window is created, spanning from the R point to the next R point and including the T wave. In consequence, using the thresholds indicated on Martínez et al [8] the beginning of the T wave is detected. The analysis on the fourth level of decomposition was made, from the wave fluctuations, as indicated on the figure 3. Between these points of inflection, crosses at zero are analyzed. If there are crossings at zero, those that are over the Martínez [8] suggested threshold, presented on the equation (1), are taken.

$$\in_T = 0.25 RMS(W(2^4 x[n])) \quad (1)$$

where, *x[n]* is the signal formed by the samples of the original ECG signal and $W(2^4 \ldots)$ refers to its fourth level of WT.

From this threshold (corresponding to 25% of the RMS value of the transform signal at the 4^{th} level of decomposition), the critic points that are considered as valid for the T wave morphology are selected. In consequence, the crossings at zero are studied to validate that the evaluated maximum corresponds to a T wave.

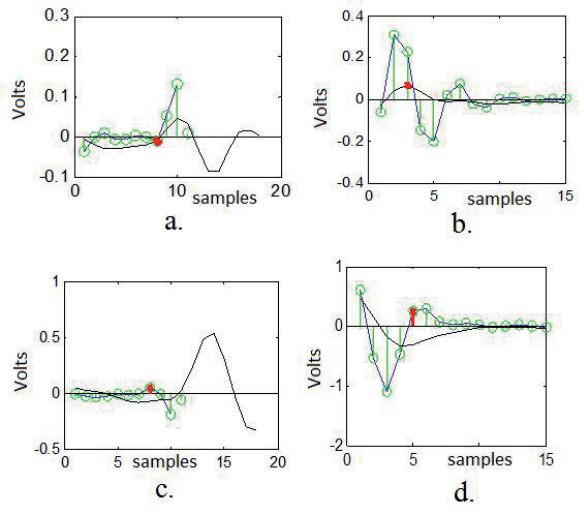

Figure 2. *Detection of the beginning and ending of the QRS complex using WT. 2a and 2c: Detection of the beginning of the QRS complex; 2b and 2d: Detection of the J point. Black line: original QRS complex, blue line second level WT.*

After determining the maximum points of the T wave, the two maximum biphasic points are confronted comparing them, discarding the one which doesn't go over the threshold in comparison to the one with the highest width.

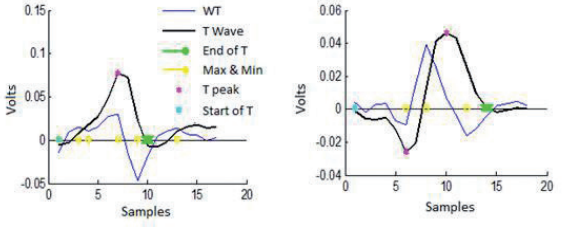

Figure 3. *Detection of T Wave Ending*

To detect the final point of the T wave, one exploration is performed after the last point considering as the T wave peak, and between the marks of maximum and minimum points. In this way, the ending of the T wave is detected. Figure 3 shows graphically the process.

The results of the algorithm show good performance with different shapes of the T wave, even in some waves where the ending is imperceptible (see figure 4). Note that in all the examples, the Q point (in red) and the T point (in magenta) are correctly detected. This detection is done adequately even with changes in the morphology of the T wave. Figure 4c presents a register with non-traditional T morphology. Figure 4d presents a biphasic T wave. In the imperceptible T wave of figure 4e, the software detects the fundamental concavity. Finally, figure 4f presents a biphasic T wave with different morphology.

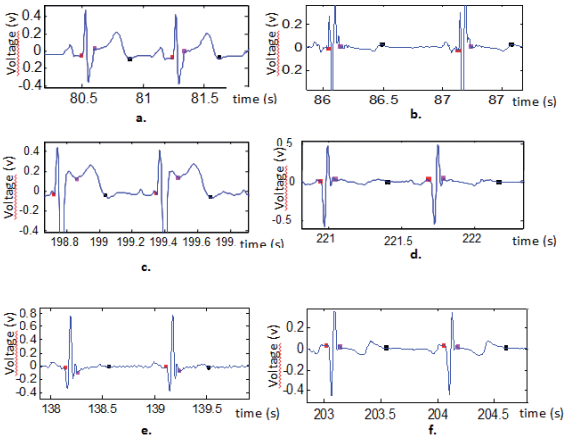

Figure 4. *QT periods detected for different cardiac signals*

C. Dispersion of the QT Interval

The dispersion of the QT interval is defined as the difference between the longest and the shortest QT intervals among the twelve classical derivations [16] [17] (see Eq. 2). Its measurement depends on the right detection of the end of the T wave (when the repolarization process finishes and the QRS starts).

$$QTd = (QT_{\max} - QT_{\min}) \qquad (2)$$

This measure shows alterations suffered by the heart related to its repolarization, due to the influence of the ANS [18]. QT dispersion is a risk factor for cardiac electrical instability and has been related to the development of malignant ventricular arrhythmias and sudden death. Some changes on the heart rate modify the QT interval duration, that's why it's very important to relate both measures, changes in heart rate and changes in time variations in the QT interval [19].

Beuve et al [20] found no significant differences in the measurement of QT dispersion if instead of calculating for 12 channels, the measurement was taken on three quasi-orthogonal channels. Niño´s work [11] has been made up a range of signals containing DI derivation, the V2 precordial and also the aVF derivation, which are quasi-orthogonal to each other, so from these, the QT segment dispersion is calculated. Figure 5 shows a semi-period of the signal in the three suggested channels, with the corresponding detection of the QT segments. From there, equation 3 allows to determine the QT segment dispersion for the respective Electrocardiographic study.

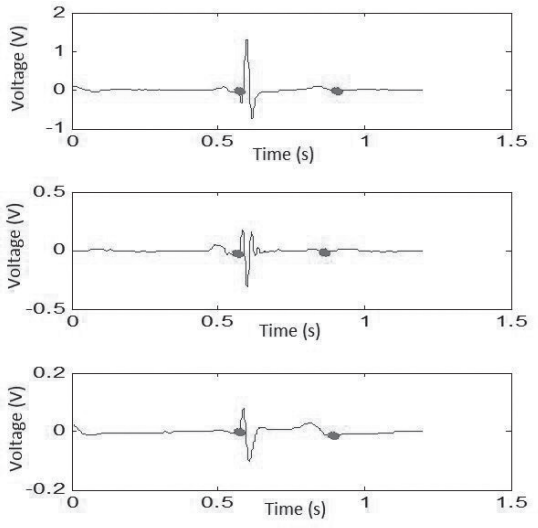

Figure 5. *Determination of the QT segment*

4. MEASUREMENT OF ANS' VARIATIONS

The study of the autonomic nervous system in the last 20 years has shown the influence that this has on the cardiovascular system.

Once the heart rate has been checked, it's possible to analyze quasi-periodic variations to different frequencies, which come from their own operation [21]. The origin of these oscillations is mediated by the sympathetic and parasympathetic systems [22] , components of the ANS. The high frequency components (HF) of this variability are related to vagal excitation (or parasympathetic), while the low frequency components (LF) show the influence of both: sympathetic and parasympathetic systems [23] .

For the estimation of HRV [9] [23], a tachogram of variational behavior of the detected R wave's half periods is constructed. From these fluctuations, spectral components of HRV are calculated, which model the behavior of the ANS and its effect on cardiac automaticity through the auricular-node.

The tachogram shown in the Figure 6 is calculated comparing each RR interval with the average RR for the full ECG record (the inverse of the heart rate's average). The tachogram has been constructed using the following steps:

- Calculation of RR intervals based on the location of the QRS complex. An RR interval is defined as the difference between the temporal location of and R landmark (R_i) and the previous one (R_{i-1}).

- Interpolation of RR time intervals with the same cardiac signal sampling, *500 Hz*. To do it, a cubic spline interpolator (4^{th} grade) is used for this interpolation, as suggested by Carvalho et al [26].

- Sub-sampling from the maximum frequency of beats physiologically possible for the subject. A sampling frequency of 5 Hz was selected as recommended by Carvalho et al [26].

In the generation of tachogram, all values coming from ectopic data [24] should receive special treatment, as these beats are not generated in the sino-atrial node, but from other cardiac fibers that produce an early beat [25]. Carvalho et al suggested softening them over the neighboring half period values, to clear the signal of extreme values hiding the actual behavior of the ANS [26].

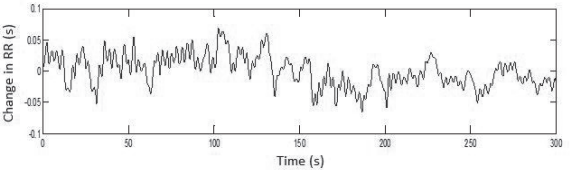

Figure 6. *Typical HRV tachogram. Values of RR duration (in seconds) are presented as variations with respect to the mean RR of all the ECG record.*

A. Calculation of Heart Rate Variability and QT variability.

In 5 minutes records, the spectral domain is usually separated into three bands [21], meanwhile for those with more than 5 minutes, it is more appropriate to use four spectral bands, as shown in Table I [12]. The software tool is able to calculate the variability in intervals of 5, 10 or 15 minutes.

Table 1. *Frequency bands*

Register < 5 min		Register >15 min	
VLF	< 0,04 Hz	ULF	<0.003
LF	0,04Hz-0,15 Hz.	VLF	0.003Hz -0.05Hz
HF	0,15Hz - 0,4 Hz.	LF	0.05Hz -0.25Hz
		HF	0.25Hz -0.4Hz

From the tachogram, a spectral components estimation is made, which shows the ANS behavior. Since the

tachogram is non-stationary, parametric identification methods are suggested. In this study, Yule-Walker's calculation is used as recommended by Gallo and Farbiarz [24]. The obtained spectrum is shown in Figure 7, for a normal subject (tachogram of Figure 6).

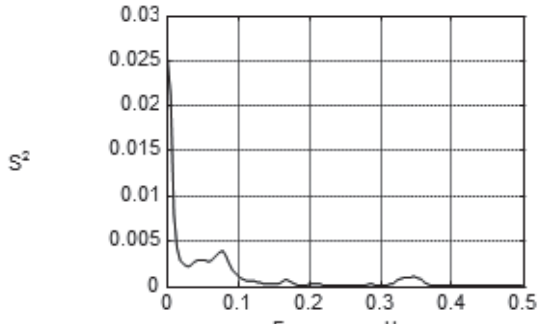

Figure 7. *HRV spectrum*

HF values are associated with the parasympathetic system, meanwhile the LF values are associated with both: sympathetic and parasympathetic components. The LF/ HF ratio is known as sympathetic-vagal response, which is important to associate the balance of the ANS operation [12].

Based on the analysis of the variation in QT segments, it's possible to discriminate if the total variability of an electrocardiographic pattern is due to the heartbeat or heart repolarization. These measures are named in the same way as for the VFC, HFQT, LFQT and their respective relationship.

5. RESULTS

To evaluate the reliability of the software and methods, a correlation of measurements between two observers was performed. The observers were previously trained to measure from the cardiac signal all the parameters previously outlined.

This comparison was validated using the intraclass correlation coefficient ICC [27], using the method proposed by Shrout-Fleiss. This is recommended for repeated measurements performed by the same judges and by using STATA SE 10.1.

To interpret ICC values, Landis and Koch [12] scale was used to qualify the agreement percentage between two observers, through six predetermined categories, where the ICC value determines the agreement percentage, as shown in Table II.

Table 2. *Concordance categories*

Poor	Low	Regular	Moderate	Substantial	Almost perfect
<1 %	1-20%	21- 40%	41- 60%	61- 80%	81- 100%

All measurements of RR variability were compared for 40 patients from the database of the stroke study [11] finding that there is an almost perfect agreement between both raters. QT variability measures agree almost perfectly, excluding LFQT / MIRRQT HFQT and whose agreement is moderate.

6. DISCUSSION

The determination of HRV have been affected because of some ectopic beats in the electrocardiographic trace, as these critically alter the construction of the tachogram and these in turn affect the calculated values for para-sympathetic and sympathetic response. Two ways for correcting these anomalies were implemented: removing the RR interval (caused by ectopic beats without compensation), or by correcting the ectopic beat time averaging time in neighboring beats (compensated ectopic beats), so the oscillations caused by the ANS can be determined.

An important topic for calculating the QT segment variability is the determination of the T wave ending. In summary, the QT variability indirectly measures the shape of the T wave. The algorithms for the detection of the T wave's end might be robust enough for very soft waves or contaminated records.

The calculation of ANS activity in its para-sympathetic and sympathetic branches, through the HRV not only involve the quantitative determination of this, but also a qualitative assessment of the physiological processes that directly and indirectly impact on cardiac dynamics.

Some processes such as breathing cause mechanical movement which changes intrathoracic pressure, disturbing venous return, cardiac output and therefore blood pressure. These changes are detected by baroreceptors, which result in alterations of the cardiac autonomic activity, triggering changes in heart rate [12].

7. CONCLUSIONS

A software tool, which is able to measure HRV, VIQT, QT dispersion, and also have some extra-tools useful for a physiologist was presented. The software serves to evaluate features of the electrocardiographic wave, identifying whether detected process are physiological or not. In turn, corrected natural events to the cardiac response but its detection involves outliers into other variations in heart rate or QT segments.

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