QTc Analysis and Comparison in Pre-Diabetic Patients

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Abstract

It has already been shown that many of the complications that we associate with diabetes appear in the patient in early stages of diabetes, or even before the disease is developed. The aim of this paper, then, is to check whether Qtc (corrected with bazett's formula) is altered in these prior stages of diabetes (insulin resistance and/or altered glucose according to the American Diabetes Association) when compared to healthy subjects.

In this paper we revisit the wavelet transform method for delineating the ECG. We use the extreme on the second (third) derivative which first appear ahead of the inflexion point of a T-wave. The algorithm detects Q waves with the first scale of a quadratic spline WT while detects the end of the T-wave by using the first derivative on the fourth (fifth) scale.

Results were obtained in our database (data acquired in the Hospital Clínico Universitario de Valladolid). This database includes 34 healthy subjects 32 pre-diabetic and 33 type 2 diabetic patients. We found QTc to be 0.3767s+/-0.03s for healthy subjects and 0.3901s+-0.03s in the case of prediabetic patients. Even though there is a sligth enlargement of the QT interval in prediabetic respect to healthy subjects, the difference in the values doesn't seem to be of statistical significance.

1. Introduction

Until recently it was considered that the autonomic neuropathy is a late complication of diabetes. However, this concept has changed. Recent results suggest that autonomic dysfunction may be present in early stages of diabetic metabolic impairment [1]. These include the so-called Metabolic Syndrome and other metabolic disorders whose common factor is insulin resistance, a decrease in the biological response to the activity of the hormone.

Diabetes mellitus is a high prevalence disease (5% of the population) in today's society, to which special attention should be paid because of the devastating impact that results in patients who suffer from it. It is the leading cause of blindness in western countries, the leading cause of lower limb amputation for non-traumatic aetiology of coronary involvement (acute myocardial infarction), stroke, kidney failure and terminal polyneuropathy. It is a public health problem of first order.

The term "Pre-Diabetes" has been revived to catalog people who do not meet the criteria for diagnosing diabetes, but whose results are not normal in the diagnostic tests. These people have a high risk of developing diabetes and also have an increased risk of a cardiovascular event. At present, the alteration of the fasting blood glucose is recognized as a diabetic pre-condition. Patients with impaired glucose tolerance are probably in a more advanced stage of pre-diabetes, have an increased risk of cardiovascular events and are a group in which the onset of diabetes can be prevented or delayed.

In people with diabetes, the neuropathy is irreversible. People with impaired glucose tolerance, a component of metabolic syndrome also are at greater risk of having this type of nerve injury. A recent study [01] in people with pre-diabetic neuropathy has shown that the affected nerve can be repaired through the right treatment and changes in lifestyle: weight loss and exercise.

QT interval is a surface ECG measure which has being subject of great research interest. Its accurate measure is very relevant as a non-invasive index of cardiac risk. This is of utility for drug toxicity quantification, VF risk assessment; Ischemic cardiopathy as in diabetes mellitus because of the increased difficulty the cells have to metabolize glucose and the related QT prolongation.

Usually a prolongation of the QT interval beyond the normal cause is associated with bad prognosis.

This is a difficult magnitude to measure mainly because the T-Wave is very smooth in its approach to the reference level.

A suitable tool to use for this task would be the discrete wavelet transform (DWT)[2][3]. The DWT is a signal analysis tool which decomposes a signal into a set of sub-signals, each of them containing, non overlapping, frequency band's information[4][5] Because of its very nature it is easy to implement by means of a filter bank, which decompose the signal in a very fast way.

The algorithm used was the “Algorithme á trous” also called redundant wavelet transform. In this implementation, each scale is obtained by using filters interpolated from the filters used in the previous scale.

2. Methods

For this study, we recruited 120 persons. We chose them in order to have 40 control patients, 40 pre-diabetic patients and 40 short evolution diabetic patients.

Exclusion criteria were chosen so that none of the subjects was under any circumstance that would yield the wrong results. So we rejected every patient who had some sort of arrhythmia, branch blockade, beta-blockers or any other medicament that alters the autonomic nervous system (ANS) or the ECG in which we are going to perform the measurements.

Each and every subject was also requested a complete blood test (glucose tolerance test included) in order to guarantee that every one of them truly belonged to the group they were assigned to. This blood test forced us to move at least 3 of our pre-diabetics into the diabetic group, and at leas 8 controls into the pre-diabetic group.

Also, after having applied the exclusion criteria and excluding the unreadable data, we ended up with 34 control subjects, 32 pre-diabetics and 33 diabetics patients. All of them normally distributed groups with no significant differences among them.

For this test, even though each patient was asked to perform a whole Ewing's battery of tests, we focused only on the ten minutes record while on rest conditions. For all of them, an ECG (8 derivations) and SCR was recorded.

A Biopac system was used to record the signals, 8 ECG derivations and SCR were recorded at a 1kHz sampling frequency

For the analysis of the data, we chose one derivation of the ECG and proceeded to measure the QT interval during the 10 minute span. Afterwards, this QT was corrected by using bazzet's formula. The intra patient mean was the parameter used in this paper.

Measure of the point where the T-wave came in contact with the isoelectric segment was made through Farina's DWT algorithm [11][12]. The use of the DWT implies the choice of a suitable mother wavelet. The wavelet we chose for our specific problem was the quadratic spline since it has already been used with good results by Li [4], Bahoura[7] and Martinez[8].

Another important reason to choose this wavelet above any other is because the filter bank associated with it behaves like a signal differentiator that works only up to a certain frequency. That is to say, the quadratic spline wavelet allows the derivation of the signal components at a given scale while ignoring all the information contained in other scales. Besides, the filters are themselves very easy to implement and very fast, computationally speaking[8][9].

Once a mother wavelet was chosen, the next step consisted in actually implementing the DWT by means of the “algorithme á trous” also called redundant transform.

Having done some tests, the adequate levels of decomposition needed in order to find the various events were assessed. For instance, the QRS complex is a 1st scale event whereas the T-wave lies in the 4th and 5th scale for its frequency range is around 4 Hz.

When the scale needed to study the T-wave was identified, a marking was made on its first local maximum or minimum, then it was differentiated again in order to obtain the second derivative of the ECG in the frequency band containing the T-wave.

Having obtained the second derivative, a search window was established in the search for the last modulus maxima (depending on the detected wave morphology). It was this point the one we identified as the ending of the T-wave [11][12], the logic behind this fact is similar to the one found in a work of Zhang[10] who in turn used a method based on mobile windows filtering which can be shown to be analogous to the double differentiation of the ECG signal.

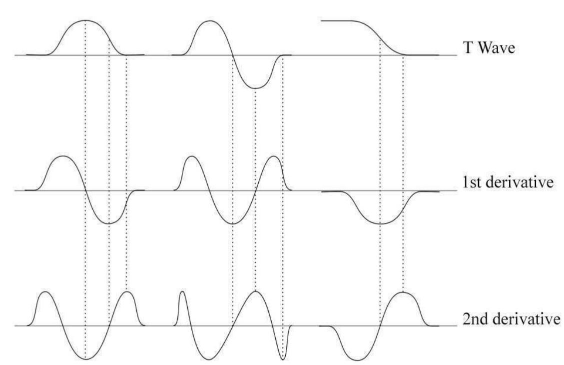

Fig. 1 Outline showing some T-wave morphologies and their derivatives.

3. Results

Once we had recorded the ECG, we proceeded to measure the position of the QRS complex with Martinez's Algoritm [8] and the T-wave positions with Farinas alternative rule [11][12].

Figure 2 shows a example of the detection performed by the algorithm for T-waves

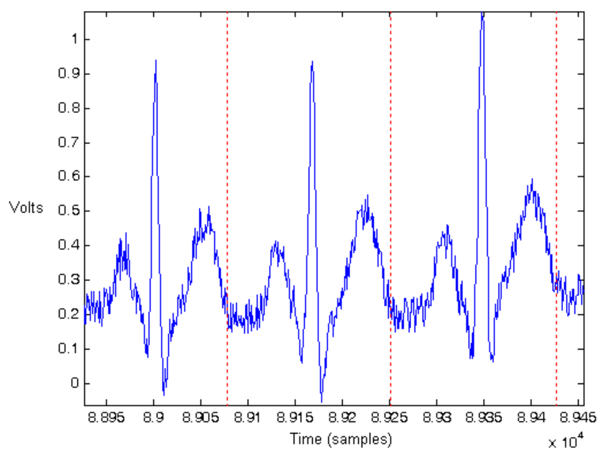

Fig. 2 Sample signal with red lines showing the detected points.

After all QT intervals were accounted for, we proceeded to correct them with Bazzet's formula in order to get corrected QT intervals. We then calculated the mean value of the QTc measured inside a patient and proceeded to compare these mean values statistically.

3.1. Statistical analysis

1.- Normality: We can accept the null hypothesis that the 3 groups are normally distributed.

Having used the Kolmogorov Smirmov and the Shapiro-Wilks test (the most suitable ones considering the size of the groups), we have obtained really high p-values (all of them above 0.20).

2.- Comparison of the means under normality conditions: We can accept the null hypothesis with any test applied:

2.1.- ANOVA: We accept the equality null hypothesis obtaining a P-value F: 0,64 for the test.

ANOVA is the most suitable way because it doesn't over inflate the error by making multiple comparisons as in other tests.

Since ANOVA needs a previous test in order to check the equality of the variance. All of the tests tried (Levene, Cochran, etc) yielded very high p-values. We can thus assume the variances to be equal .

2.2.- Kruskal-Wallis's test:We accept the equality null hypothesis of the 3 means; p-value=0.73.

This is a non-parametric test used as an alternative to ANOVA and can be used when the normality or the variances cannot be deemed as equal.

2.3.- Unilateral specific means comparation:

a) Diabetics Vs Prediabetics

- Student's t Test: p-value=0,57.
- Non-parametric Wilcoxxon-Mann-Whitney test: p-valor=0,58.

b) Diabetics Vs Controls

- Student's t Test: p-value=0,21.
- Non-parametric Wilcoxxon-Mann-Whitney test: p-valor=0,26.

c) Prediabetics Vs Controls

- Student's t Test: p-value=0,20.
- Non-parametric Wilcoxxon-Mann-Whitney test: p-valor=0,25.

4. Discussion and conclusions

In short, the 3 groups don't show a significant statistical differences greater the that found in random groups (according to the tests we made).

In other words, the variable Qtc doesn't seem to be able to differentiate the 3 study groups.

Yet, since there are reasons to believe that such a difference could be found, we propose to enlarge the study groups since our groups are very little.

We could infer, that in the case of controls Vs diabetics, with the differences in means that we have and the current sigma estimation, the differences observed would have been significative to the 0.005 level given that the groups were composed of at least 133 subjects each.

Yet, we cannot guarantee that the current difference in the means is going to be kept in larger groups.

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"Aplicación de Técnicas de Procesamiento de Señal para el Desarrollo de Herramientas de Diagnóstico de la Neuropatía Vegetativa".

References

[1] Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, Heiss G. Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care. 28(3):668-74. 2005.

[2] Xue J, Chen Y, Gao W, Han X, Rowlandson I. Alternate gold standard of QT-interval and T-wave morphology measurements: a modeling approach. Journal of Electrocardiology. 2007;40(6, Supplement 1)

[3] Sörnmo L, Laguna P. Bioelectrical Signal processing in Cardiac and Neurological Applications. Elsevier Academic Press, 2005 (ISBN: 0-12-437552-9).

[4] Li. C, et al. Detection of ECG Characteristic Points Using Wavelets Transform. IEEE Transactions on Biomedical Engineering (1995) ., Vol 42, pp 21-28.

[5] Almeida R, Martinez JP, Rocha AP, Olmos S, Laguna P. Improved QT variability quantification by multilead automatic delineation. In: Computers in Cardiology, 2005; 2005. p. 503-506.

[6] http://www.physionet.org/physiotools/ecgsyn/

[7] Bahoura. M, et al. DSP implementation of Wavelet Transform for Real Time ECG Wave Forms Detection and Heart Rate Analysis (1997), Computers meth. Programs Biomed., N 52. pp.35-44.

[8] Martinez. J.P, et al. A Wavelet-Based ECG Delineator: Evaluation on Standard Databases (2004). IEEE Transactions on Biomedical Engineering vol 51, N4. pp. 570.

[9] Chen PC, Lee S, Kuo CD. Delineation of T-wave in ECG by wavelet transform using multiscale differential operator. IEEE Trans Biomed Eng. 2006 July;53(7):1429-1433.

[10] Zhang Q, Manriquez AI, Médigue C, Papelier Y, Sorine M. An algorithm for robust and efficient location of T-wave ends in electrocardiograms. IEEE Trans Biomed Eng. 2006 December;53(12 Pt 1):2544-2552.

[11] Rivera Farina, P. V., P. Laguna, J. P. Martinez, J. Perez Turiel, A. Herreros Lopez, and S. Wong (2008, September). An alternative decision rule for threshold based t-wave measurement algorithms based on second derivative extrema. In *2008 Computers in Cardiology*, pp. 709-712. IEEE.

[12] Rivera Farina, P. V., J. Pérez Turiel, and A. Herreros López (2008). Aplicación de la transformada wavelet para el desarrollo de un método computacionalmente simple de detección del final de la onda t. In C. Müller-Karger, S. Wong, and A. Cruz (Eds.), *IV Latin American Congress on Biomedical Engineering 2007, Bioengineering Solutions for Latin America Health*, Volume 18, Chapter 40, pp. 171-174. Berlin, Heidelberg: Springer Berlin Heidelberg.

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