Study of Cardiac Repolarization during Oral Glucose Tolerance Test in Metabolic Syndrome Patients

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Abstract

QT interval could be relevant for cardiopathy assessment in metabolic syndrome (MS) because of the increased difficulty the cells have to metabolize glucose, thus possibly prolonging QT intervals.

The aim of this paper is to explore whether QT interval is altered in MS patients during the Oral Glucose Tolerance Test (OGTT). This database includes 10 healthy subjects and 15 MS patients undergoing OGTT. The ECG recordings were performed at sampling frequency of 1000 Hz, 16 bit resolution and 12-lead records. Each data set includes: 15 minutes ECG signal acquisition before the OGTT and before each blood samples extraction (30, 60, 90, 120 minutes).

The wavelet transform method was used for delineating the ECG in this work. In order to find the end of T-wave, an alternative to threshold methods was used. This variation finds the extreme on the third derivative, which first appears ahead of the local maxima of a T-wave.

The mean and the standard deviation (STD) of all QTc were calculated in each record. It was found a slight enlargement of the QT interval in MS respect to healthy subjects, however the difference doesn't seem to be of statistical significance. Yet, MS patients show a significant decrease in their STD respect healthy subjects.

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 (MS) 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 etiology of coronary involvement (acute myocardial infarction), stroke, kidney failure and terminal polyneuropathy. It is a public health problem of first order.

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 (mainly 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 25 persons. We chose

them in order to have 10 control patients and 15 MS patients, age between 20 and 44 years old, who fulfilled the following conditions:

- Non-smokers.
- Not under medical treatment.
- No disabilities.
- No known cardiovascular diseases.

MS presence was assessed by the "National Cholesterol Education Panel's Adult Treatment Program III" (NCEP ATP III) which means that every MS patient had at least two of the following:

- Waist circumference > 102cm for men
- Waist circumference > 88cm for women
- Blood pressure > 130/85 mmHg
- HDL < 40 mg/dL for men
- HDL < 50 mg/dL for women
- Fasting glucose level > 110mg/dL
- Triglycerides > 150mg/dL

A 12 lead ECG was recorded for each patient during the 15 minutes prior to each blood extraction during an oral glucose tolerance test (OGTT).

For the analysis of the data, we measured the mean QT interval for each recording. The first Q detected in any lead was paired with the last T ending found in order to have a global QT interval. Afterwards, this QT was corrected by using Bazzet's and Fridericia's formula.

Measure of the point where the T-wave came in contact with the isoelectric segment was made through Farina's DWT algorithm [11][12][13]. 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 1^{st} scale event whereas the T-wave lies in the 4^{th} and 5^{th} 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][13].

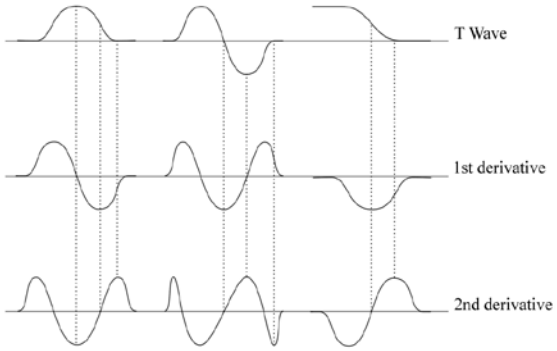

Fig. 1: Outline showing some T-wave morphologies and their derivatives.

3. Results

Five 15-minute recordings were obtained for each individual (at rest, 30, 60, 90 and 120 minutes after the glucose intake). QT interval was calculated for every beat in every record and corrected by both, Bazzett's and Fridericia's formula, finally a mean was calculated for each record.

The mean and the standard deviation (STD) of all QTc were calculated in each record. It was found a slight enlargement of the QT interval in MS respect to healthy subjects, however the difference doesn't seem to be of statistical significance. Yet, MS patients show a significant decrease in their STD respect healthy subjects. According to Bazzet's correction 33ms in controls vs. 13 ms in MS; and according to Fridericia's formula 26ms in controls vs. 10ms in MS in the resting phase.

This translates in intra-register reduced variations in SM patients respect to their healthy counterparts. This makes us think that metabolic syndrome patients might show reduced QT variability just as they show reduced heart rate variability. QTc, on the other hand, didn't seem to vary during the test.

Sample MS	Bazzett QTc	STD	Fridericia QTc	STD
Resting	0.346	0.013	0.337	0.010

30 min	0.354	0.025	0.343	0.020
60 min	0.351	0.020	0.342	0.016
90 min	0.351	0.022	0.341	0.018
120 min	0.349	0.019	0.339	0.015

Sample control	Bazzett QTc	STD	Fridericia QTc	STD
Resting	0.336	0.033	0.331	0.026
30 min	0.345	0.034	0.340	0.027
60 min	0.341	0.025	0.337	0.019
90 min	0.340	0.023	0.337	0.019
120 min	0.338	0.025	0.334	0.019

Tables 1 and 2. QTc results in MS patients and control subjects.

It can be seen from the result on the tables that QTc doesn't vary among phases in neither group. Nor can a statistical difference be observed between groups.

Regarding the dispersion of the QTc, a great difference can be observed, specially at resting conditions. MS patients show a reduced dispersion in their intervals, meaning that they have a really reduced variability in their QTc intervals in comparison with control subjects.

Another interesting trend can be observed in figure 2. Should we consider the OGTT as an autonomic stimulus, control subjects show an obvious trend towards a decrease in QT variability as the stimulus evolves whereas in MS patients the trend is reversed, starting with a really diminished variability before the glucose intake, which increases in response to the intake.

The same trend can be observed by applying Fridericia's formula as can be seen in figure 3.

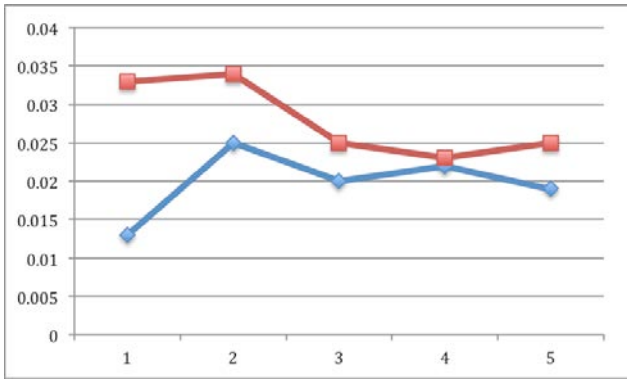

Fig. 2. Dispersion of measurements between groups for each phase (control in red and MS in blue, Bazzet's correction).

4. Discussion and conclusions

Metabolic Syndrome group a series of disorders that, if not properly treated, degenerate in diabetes which, in turn, carries an associated autonomic dysfunction. A sign of autonomic activity is the QT interval and its variability.

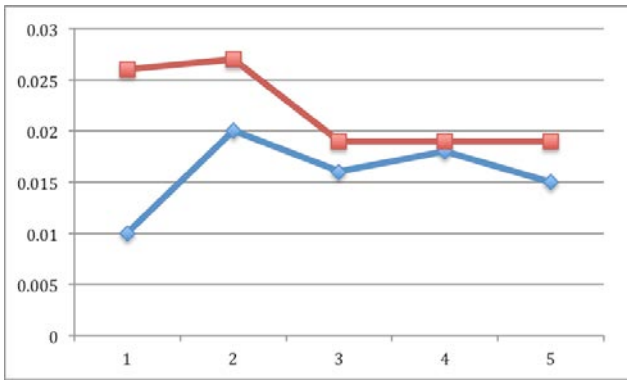

Fig. 3: Dispersion of measurements between groups for each phase (control in red and MS in blue, Fridericia's correction).

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Data show signs of early autonomic dysfunction even if it is considered a late complication of diabetes. The steep difference in variability between groups could be considered a clear sign of early autonomic impairment in MS patients if the groups were the appropriate size to be of statistical significance. This difference is at maximum in the resting phase and decreases with time during the glucose intake.

No QT prolongation could be observed between groups as opposed to studies made with long term evolution diabetic patients, which points us to believe that autonomic dysfunction can first be observed through altered variability that through QT prolongation (which in turn could point to an earlier parasympathetic damage prior to the sympathetic one).

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