Ventricular Repolarization in Diabetic Patients: Characterization and Clinical Implications

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Abstract

Background: Diabetes mellitus is a chronic and very common condition, and there has been lately a considerable increase in its prevalence and incidence. Diabetic patients have increased cardiovascular mortality, in which malignant ventricular arrhythmias seem to be implicated.

Objective: To study the effects of diabetes on ventricular repolarization parameters responsible for an increased susceptibility to malignant ventricular arrhythmias and/or sudden death.

Methods: We selected a group of 110 diabetic patients and a group of 110 controls with the same distribution of age, gender and race. We evaluated the following parameters of ventricular repolarization: QTmax, QTmean, QTmin, QTcmax, QTcmean, QTcmin and QTc dispersions, Tpeak-Tend and jTpeak-jTend intervals (DII, V2 and V5), Tpeak-Tend and jTpeak-jTend dispersions. The electrocardiograms (ECG) were performed by the same operator and reviewed by the same observers. QT intervals were corrected according to Bazzet’s formula.

Results: We found significantly higher values of QTcmax (p < 0.001), QTcmean (p < 0.001), QT dispersion (p < 0.001), QTc dispersion (p < 0.001), Tpeak-Tend dispersion (p < 0.001), and jTpeak-jTend dispersion (p < 0.001) in diabetic patients than in controls. In diabetic patients, we observed prolonged values of QTc interval (5.5%), QT dispersion (0.9%), QTc dispersion (0%), Tpeak-Tend interval (7.3%), jTpeak-jTend interval (6.4%), Tpeak-Tend dispersion (16.4%), and jTpeak-jTend dispersion (12.7%). In the controls there were no prolonged values of any of the parameters.

Conclusion: We concluded that diabetes causes prolongation and spatial dispersion of repolarization, and it may contribute to a greater ventricular electrical instability, whose expected clinical expression may be malignant ventricular arrhythmias. (Arq Bras Cardiol. 2012; [online].ahead print, PP .0-0)

Keywords: Arrhythmias cardiac; diabetes mellitus; electrocardiography; death; sudden; cardiac.

Methods

Sample

We conducted a cross-sectional study based on a sample of 220 individuals, of whom 110 were diabetic and 110 healthy individuals (by clinical and laboratory evaluation) selected for pairing. Of the 110 individuals with the disease, 106 had type 2 diabetes, and 4 had type 1 diabetes.

Data collection was performed at the Department of Cardiology of the Personalized Healthcare Units (UCSP) of Salvaterra de Magos and of Marinhais, in Portugal.

Inclusion criteria encompassed all individuals diagnosed with diabetes mellitus; however, we excluded all patients with chronic atrial fibrillation, atrial flutter, left/right bundle branch block, pre-excitation syndromes, patients with pacemakers, drug addicts, and dialysis patients. We also excluded patients treated with drugs that prolong the QT interval, as suggested by the European Society of Cardiology (ESC).

The study is in compliance with the Declaration of Helsinki and was approved by the ethics committees of all UCSPs involved. All study subjects signed an informed consent form.

Procedure

To obtain the sample, we initially accessed the list of diabetic patients enrolled in Salvaterra de Magos, and the inclusion criteria were established.

We conducted a simple 12-lead ECG in all diabetic patients. The ECG was always performed with the patient supine, at rest, at a paper speed of 50 mm/s and voltage of 10 mm/mV. To make the ECGs we used the electrocardiograph Cardiolime–Delta 1 Plus®, in the UCSP of Salvaterra de Magos, and the electrocardiograph NIHON KOHDEN ECAPs 12-ECG 8119K®, in the UCSP of Marinhais. For the control group we also conducted simple 12-lead electrocardiograms under the same conditions and measurements used for the diabetic patients. The control subjects were required to have a normal
ECG and to be healthy in the clinical assessment and the physical examination, with no pathologic processes that might affect ventricular repolarization. To this end, we conducted a consultation of the clinical process and only one ECG of the individuals that met the desired criteria. The control group was selected by pairing, allowing an adjustment of the two groups for age, gender, and ethnicity.

For the analysis of the ECG, we performed a manual measurement of the values using a digital caliper with measuring range of 0-150 mm, 0.01 mm resolution, and 0-100 ± 0.02 mm accuracy. The value obtained was converted to milliseconds (ms). We considered the T-wave peak as the steepest point, and the T-wave end as the point of return to the baseline. The T-wave end was obtained by the intersection point of the tangent line of the terminal portion of the T-wave with the isoelectric line. When the U-wave was present, the T-wave end was considered as the nadir between the T-wave and the U-wave. The derivations in which it was not possible to define the T-wave end due to low voltage were discarded.

Measurement of the QT interval (the interval from the start of the QRS complex to the end of the T-wave) was performed in all 12 leads, and the longest and the shortest intervals measured were selected. QT interval dispersion was obtained by the difference between the maximum and the minimum QT intervals found in the 12-lead electrocardiogram.

Measurement of the QTpeak (the interval from the start of the QRS complex to the peak of the T-wave) was conducted in DII, V5, and V6 leads. Measurement of the QTend (the interval from the start of the QRS complex to the end of the T-wave) was also conducted in DII, V5, and V6 leads. The Tpeak-Tend interval was obtained by the difference between the QTend and the QTpeak.

The QT interval was also corrected according to Bazett’s formula which consists in dividing the measured QT by the square root of the RR interval (QTc = QT/√ RR), thus providing the QT interval value adjusted for heart rate.

The QTc dispersion was obtained by the difference between the highest and the lowest values of QTc in the 12 leads of the ECG.

According to internationally accepted guidelines, the QTc interval was considered prolonged when higher than 440 ms for male patients, and higher than 460 ms for female patients. The QT dispersion was considered prolonged when higher than 65 ms, according to other previously conducted studies.

Measurement of the Tpeak-Tend (the interval from J point to the peak of the T-wave) was conducted in DII, V5, and V6 leads. Measurement of the Tend-Tpeak (the interval from the start of the QRS complex to the end of the T-wave) was also conducted in DII, V5, and V6 leads. The Tpeak-Tend interval was obtained by the difference between the Tend and the Tpeak.

The Tpeak-Tend interval dispersion was obtained by the difference between the largest and the smallest intervals in DII, V5, and V6 leads.

The Tpeak-Tend interval was considered prolonged when greater than 100 ms, and the Tpeak-Tend dispersion was considered prolonged when higher than 20 ms, as suggested by other studies.

The ECG was obtained, the measurements were repeated by a third observer with expertise in electrocardiographic analysis.

The body mass index (BMI) was divided into several classes as proposed by the World Health Organization (WHO). Hypertension was divided into several classes according to the recommendations of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Reference values for biochemical parameters used in this study were those recommended by the Massachusetts General Hospital.

Statistical Analysis

The collected data were entered in the software SPSS for Windows, version 18.0, which performed a statistical analysis. The distribution of variables was tested for normality using the Kolmogorov-Smirnov test, and the heterogeneity of variances was evaluated by Levene’s test. A simple descriptive analysis was performed for the general characterization of the sample and distribution of variables.

Differences between groups were analyzed using the Student t test for independent samples. Categorical data were analyzed using the chi-square (X²) test. The correlations between variables were analyzed using Pearson’s correlation coefficient (r).

Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as frequency (%).

A p value <0.05 was considered statistically significant for a confidence interval of 95%.

Results

Sample Characterization

The sample used for this study involved the same number of diabetic patients (n = 110) and controls (n = 110). All individuals in the sample were Caucasian. In both groups there was a slight predominance of males, but no statistically significant differences (p = 0.063) were observed. The proportion of men in both groups was 54.5%, and 45.5% for women. As expected, there were no statistically significant differences in age between the diabetic group and the control group (mean age 67.35 ± 9.20 years versus 65.99 ± 8.99 years, respectively, p = 0.260).

The diabetic group had a mean BMI significantly higher than the control group (28.38 ± 3.69 kg/m² versus 26.77 ± 3.13 kg/m², p = 0.001). In both cases, the average BMI was above the upper limit of normality suggested by WHO. BMI values classified according to the degree of obesity were compared between diabetic patients and controls. The results showed that a high percentage of diabetic patients and controls had pre-obesity (47.3% and 60.7% respectively), with a reduction in the proportion of individuals as the BMI increased in both groups. In the three degrees of obesity, there was always a higher percentage of diabetic patients, and in underweight, normal weight and pre-obesity categories, there were greater
proportions of controls. The differences in the distribution of individuals in each group by BMI classes were significant, and in the diabetic group there was a greater relative proportion of patients with weight above the upper limit of normal.

Regarding the type of diabetes identified in patients included in the diabetic group, most had type 2 diabetes (96.4%), and the others had type 1 diabetes (3.6%). The mean age at diagnosis was 55.10 ± 12.38 years, and currently the mean duration of the disease is 12.25 ± 9.59 years.

With regard to blood pressure values, the diabetic group had an average systolic blood pressure of 141.76 ± 14.11 mmHg, and a mean diastolic blood pressure of 78.05 ± 10.25 mmHg. The average systolic blood pressure was slightly above the upper normal limit; however, the average diastolic blood pressure was within normal range. All controls had values of systolic and diastolic blood pressure within normal limits.

With the classification of blood pressure in the various degrees of hypertension, it was observed that the largest percentage of diabetic patients had blood pressure situated at the level of grade 1 hypertension (48.2%). The percentage of diabetic patients gradually decreased in higher grades of hypertension (15.5% in grade 2 to 0.9% in grade 3). The proportion of diabetic patients with hypertensive blood pressure values was greater than the proportion of diabetic patients with normal blood pressure values (64.6% versus 35.5%, respectively).

Regarding biochemical parameters, the diabetic group had an average glucose value of 153.72 ± 55.63 mg/dL, an average HbA1c value of 7.11 ± 1.56%, an average HDL cholesterol value of 49.99 ± 12.98 mg/dL, an average total cholesterol value of 180.45 ± 38.55 mg/dL, an average triglycerides value of 153.15 ± 118.49 mg/dL, and an average creatinine value of 1.07 ± 0.42 mg/dL. The average values of glucose and HbA1c were slightly increased, but the other parameters were normal. All controls had normal biochemical parameters.

Regarding harmful habits, 16.4% of diabetic patients had a habit of drinking alcohol, and 7.3% had an active smoking habit. None of the diabetic patients consumed drugs.

The complication with the highest proportion of diabetic patients was cerebrovascular accident (CVA) (12.7%), followed by blindness (4.5%), myocardial infarction and terminal renal failure (1.8% each), and amputation above the ankle (0.9%). The disease most often associated with diabetes was hypertension (76.4%), followed by dyslipidemia (61.8%), nephropathy (49.1%), retinopathy (42.7%), nephropathy (31.8%), coronary heart disease (14.5%), and heart failure (3.6%).

### Comparative Analysis

We conducted a comparative analysis between diabetic patients and controls, of the following parameters: QT and QTc intervals, QT and QTc dispersions, Tpeak-Tend and jTpeak-jTend intervals, and Tpeak-Tend and jTpeak-jTend dispersions.

### QT and QTc intervals

Table 1 shows the comparison of the mean values of the maximum, minimum and mean QT and QTc intervals between diabetic patients and controls. The results showed that the mean QT\text{max} and QT\text{mean} intervals are higher in diabetics when compared with controls, though with no significant differences (p = 0.10 and p = 0.874 respectively). The average QT\text{max} interval was lower in diabetic patients compared with controls, but also with no significant differences (p = 0.161). When the QT interval was corrected for heart rate, the mean QTc\text{max}, QTc\text{mean} and QTc\text{cmin} intervals were higher in diabetics than in controls however, significant differences between diabetic patients and controls were found only in QTc\text{max} and QTc\text{mean} (p < 0.001 for both). In this study, we found only 5.5% of diabetic patients with a prolonged QTc interval; however, none of the controls had a prolonged QTc interval.

### Dispersion of QT and QTc

Figure 1 shows the comparison of the mean QT and QTc dispersions between diabetics and controls. The results showed that diabetics have a significantly higher mean QT dispersion than controls (27.49 ± 10.10 versus 15.73 ± 4.18 ms, p < 0.001). Using the QT dispersion corrected for heart rate, we observed that the differences remained higher in diabetic patients when compared with controls (29.92 ± 10.57 versus 16.68 ms ± 4.48 ms, p < 0.001). A prolonged QT dispersion was found in only 0.9% of diabetics, but we did not find in any of the controls a prolonged QTc dispersion. No prolonged QTc dispersion was found in any diabetic patient or control.

### T\text{peak}-T\text{end} and jT\text{peak}-jT\text{end} intervals

Regarding the comparison of T\text{peak}-T\text{end} and jT\text{peak}-jT\text{end} intervals, Table 2 summarizes the results in diabetics and controls. There were no statistically significant differences in any of the comparisons made. Comparing the frequency of subjects with a prolonged Tpeak-Tend interval (above the cut-off limit determined for the study), the results showed that 7.3% of diabetic patients had a prolonged T\text{peak}-T\text{end} interval, which was not observed in any of the controls. A prolonged

### Table 1 – Comparison of mean QT and QTc intervals between diabetics and controls

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|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| QT interval (ms)               | Total           | Diabetics       | Controls        | p               |
| QT\text{max}                   | 376.65 ± 29.54  | 379.89 ± 33.07  | 373.41 ± 25.26  | 0.103           |
| QT\text{min}                   | 365.84 ± 28.32  | 366.15 ± 31.36  | 365.54 ± 25.05  | 0.874           |
| QT\text{mean}                  | 355.04 ± 27.90  | 352.40 ± 30.40  | 357.67 ± 25.01  | 0.161           |
| QTc interval (ms)              |                 |                 |                 |                 |
| QTc\text{max}                  | 404.51 ± 24.69  | 413.70 ± 28.10  | 395.31 ± 16.28  | < 0.001         |
| QTc\text{mean}                 | 392.86 ± 22.79  | 396.74 ± 26.64  | 386.97 ± 16.25  | < 0.001         |
| QTc\text{cmin}                 | 381.21 ± 22.00  | 383.78 ± 26.18  | 378.63 ± 16.54  | 0.083           |

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Dispersion of $T_{\text{peak}}$-$T_{\text{end}}$ and $J_{\text{peak}}$-$J_{\text{end}}$

Figure 2 shows the comparison of the mean $T_{\text{peak}}$-$T_{\text{end}}$ and $J_{\text{peak}}$-$J_{\text{end}}$ dispersions between diabetics and controls. The results showed that diabetics had a mean $T_{\text{peak}}$-$T_{\text{end}}$ dispersion significantly higher than controls ($13.05 \pm 9.36$ ms versus $5.07 \pm 3.26$, $p < 0.001$). Using the $J_{\text{peak}}$-$J_{\text{end}}$ dispersion, we observed that differences remained higher in diabetic patients, when compared with controls ($12.70 \pm 5.13$ versus $10.28$ ms $\pm 4.05$ ms, $p < 0.001$). In this study, we found only 16.4% of diabetics with a prolonged $T_{\text{peak}}$-$T_{\text{end}}$ dispersion, but it was not observed in any of the controls.

Correlational Analysis

We studied the correlation of gender, age, body mass index, duration of diabetes, systolic and diastolic blood pressure, glucose, HbA1c, total and HDL cholesterol, triglycerides, creatinine, previous cardiovascular events such as stroke, myocardial infarction, stable and unstable angina, with different electrocardiographic parameters. In the bivariate and multivariate analysis, there were no significant correlations between variables.

Discussion and Conclusion

The QT interval is the most used parameter in the electrocardiographic assessment of repolarization and its prolongation is associated with increased risk of arrhythmogenesis. Therefore, in our study, we considered it important to assess this parameter in diabetes, in order to assess the potential risk in these individuals. When comparing the QT interval between diabetics and controls, no significant differences were found; however, the QT interval does not take into account the heart rate and, therefore, these results had no clinical relevance. However, after correcting the QT interval for heart rate using the formula of Bazett, we found significant differences between diabetics and controls, and the $\text{QTc}_{\text{max}}$ and the $\text{QTc}_{\text{mean}}$ intervals were significantly higher in diabetics. We found several studies that analyzed the $\text{QTc}_{\text{max}}$
The QT dispersion is a parameter that represents the spatial dispersion of repolarization and evaluates the heterogeneities of repolarization, and it is used as an indication of electrical instability and as a marker of arrhythmogenic risk. In our study, when comparing diabetics with controls, we observed significant differences in QT dispersion. The QT dispersion was significantly higher in diabetic patients when compared with controls. When this dispersion was corrected for heart rate, the results were identical, suggesting that the QTc dispersion is a parameter that does not add greater clinical relevance to QT dispersion in the risk stratification of patients with diabetes. The small differences between QT and QTc dispersions are probably due to the inaccuracy of correction values for heart rate, since the greater the QT dispersion, the greater the difference between the two, and vice versa. Several studies have found a significantly greater QT dispersion in diabetics when compared with controls. Others have found an also significantly higher QTc dispersion in diabetic patients when compared with controls. However, one study found no significant differences in QT dispersion between diabetics and controls.

The Tpeak-Tend interval is a parameter that reflects the transmural dispersion of repolarization, since its prolongation is associated with an increased arrhythmogenic risk. In this study, the Tpeak-Tend and the JTpeak-JTend intervals of diabetics were similar to those measured in controls, with no significant differences. One of the reasons for these results may have been the use of only three leads (DII, V5, and V6), which although providing a substantially orthogonal assessment (XYZ) may not be sufficient to evaluate the transmural dispersion represented by the Tpeak-Tend interval.

The Tpeak-Tend dispersion and the JTpeak-JTend dispersion also characterize the regional variation of the transmural dispersion, and their prolongation is also associated with an increased arrhythmogenic risk, so they are used as markers for the risk of arrhythmogenesis. However, we found no study on the dispersion of these intervals in diabetics. Although the mean values were similar in DII, V5, and V6 leads, our study showed that diabetics had Tpeak-Tend and JTpeak-JTend dispersions significantly higher than the controls.

Gupta et al. investigated a new risk marker that was not analyzed in our study, the Tpeak-Tend/QT ratio, which showed increased values in patients with arrhythmic events who had Brugada syndrome, short QT syndrome, and long QT syndrome, and also in patients with organic heart disease, such as myocardial infarction. A further investigation of the usefulness of this parameter in the identification of diabetics at higher risk of arrhythmogenesis would be an added advantage.

These changes in ventricular repolarization in diabetic patients are caused by several clinical disorders and/or pathological conditions associated with diabetes, such as hypertension, dyslipidemias, hyperglycemia, hypoglycemia, coronary disease, neuropathy, nephropathy, heart failure, etc. These conditions are responsible for the onset of metabolic disorders, electrolyte disturbances, imbalances of the autonomic nervous system, structural changes, myocardial fibrosis resulting in longer dispersion and/or repolarization time.

Although repolarization parameters were significantly higher in diabetic patients than in controls, the percentage of diabetics with values above normal was relatively small for all parameters. The fact that few diabetics had abnormal values of repolarization...
parameters indicates that these individuals may have been at relatively low risk of arrhythmia, confirming a good clinical orientation of these patients by the physicians involved. However, it is still important to emphasize that significant differences were observed in a number of parameters evaluated when compared with the control group, indicating that the repolarization in diabetic patients, even if well-controlled in therapeutic terms, was more heterogeneous than that observed in non-diabetic individuals. Moreover, it is worth mentioning that a large proportion of the diabetic patients evaluated had a relatively short duration of illness, and the effects of the disease might not have been sufficiently established to produce greater prolongation of repolarization parameters.

Another fact of great importance is the influence of medication on several electrocardiographic parameters, because there are numerous drugs that cause prolongation and/or dispersion of repolarization. This study excluded individuals receiving medications that are more frequently associated with repolarization changes; however, there was no absolute guarantee that all other medications had no influence on repolarization. In fact, a study by Costa et al. evaluated the influence of metformin (a drug commonly used in diabetics to control blood glucose) on QT interval and QT dispersion in diabetic rats. The results showed that, with low and moderate doses of metformin, there were significant changes in electrocardiographic parameters, but this did not happen when the dose was high. Although no study was conducted in humans, it remains plausible that this result can be identical in diabetic humans, as in diabetic rats. This aspect is particularly relevant in this study since most patients included were treated with metformin.

Furthermore, this study showed a statistically significant difference in BMI between diabetics and controls. However, there were no significant correlations between BMI and repolarization parameters, which led us to conclude that obesity had no significant influence on the various repolarization parameters evaluated. On the other hand, in diabetic patients, systolic blood pressure, diastolic blood pressure, glucose, HbA1c, total cholesterol, HDL cholesterol, triglycerides and creatinine do not appear to significantly influence the repolarization parameters evaluated, since there were no significant correlations between them. These results may not be clinically relevant, since they were obtained from a punctual measurement.

This study was not without limitations. A larger sample would certainly increase the statistical power of the study, and probably some differences would therefore become more expressive. Moreover, manual measurements of intervals without the support of any technology that could ensure a more precise measurement may also be an aspect to be taken into account. The accuracy and reproducibility of measurements of repolarization parameters were limited by difficulties in identifying the end of the T-wave in some cases. One other problem encountered was the lack of a consensus on the values of several normal electrocardiographic parameters. Another drawback was the electrocardiographic recording done in groups of 3 simultaneous leads, since a record of 12 simultaneous leads would allow a more accurate measurement of several repolarization parameters in the same cardiac cycle.

Despite some methodological limitations, this study clearly demonstrated a relationship between diabetes and changes in a set of electrophysiological parameters that indicate a prolonged and more heterogeneous repolarization in these patients, when compared with healthy subjects. This fact may be involved in the greater vulnerability of these patients to cardiac arrhythmias. Therefore, the assessment of these new markers for arrhythmogenic risk may be important for better risk stratification of diabetic patients, a conclusion that needs confirmation in larger prospective studies.

Potential Conflict of Interest
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