A wearable remote monitoring system for the identification of subjects with a prolonged QT interval or at risk for drug-induced long QT syndrome
A wearable remote monitoring system for the identification of subjects with a prolonged QT interval or at risk for drug-induced long QT syndrome

Silvia Castelletti a, Federica Dagradi a, Karine Goulene b, Aurora I. Danza c, Enrico Baldi c, Marco Stramba-Badiale b, Peter J. Schwartz a,⁎

a Center for Cardiac Arrhythmias of Genetic Origin, IRCCS Istituto Auxologico Italiano, Milan, Italy
b Department of Geriatrics and Cardiovascular Medicine, IRCCS Istituto Auxologico Italiano, Milan, Italy
c Department of Molecular Medicine, University of Pavia, Pavia, Italy

A R T I C L E   I N F O

Article info

Received 20 February 2018
Received in revised form 15 March 2018
Accepted 19 March 2018

Keywords:
Drug-induced long QT syndrome
Congenital long QT syndrome
Torsades-de-Pointes
I k-blocking drugs
QT interval
Sudden death

A B S T R A C T

Background: A correct measurement of the QT interval in the out-of-hospital setting is important whenever the long QT syndrome (LQTS) is suspected or a therapy might lead to drug-induced LQTS (diLQTS) because QT interval monitoring in the initial days of therapy could alert to dangerous QT prolongation. We explored whether automated QTc measurements (BGM) by BodyGuardian™ (BG), a wearable remote monitoring system, are sufficiently reliable compared to our own manual measurements (MM) performed on the same beats during 12 lead Holter recordings in LQTS patients (pts) and in healthy controls.

Methods: We performed 351 measurements in 20 LQTS pts and 16 controls. MM and BGM were compared by a Bland-Altman plot (BAp). High values of BAp indicate large differences between measurements.

Results: In all 36 subjects QTc was 446 ± 41 and 445 ± 47 ms in MM and BGM, respectively. The mean ± SE BAp was −1.4 ± 1.8 ms for QTc in all subjects, 8.3 ± 2.3 and −7.2 ± 2.5 ms respectively in controls and LQTS. The disagreement between BGM and MM <15 ms in all, in controls, and in LQTS was respectively 57%, 63% and 54%. Among controls, there were only 3/132 false positive measurements (BGM QTc >470 ms when MM QTc <440 ms) in 3 different subjects. Among LQTS, there were 10/219 false negative measurements (BGM QTc <440 ms when MM QTc >470 ms) in 6 pts, but only two had multiple false negative values.

Conclusions: This wearable monitoring system reliably identifies a prolonged QT interval and probably also subjects at risk for diLQTS.

© 2018 Elsevier B.V. All rights reserved.

1. Introduction

A prolonged QT interval can be the expression of an inherited cardiac disease, Long QT Syndrome (LQTS), or the adverse effect of a medication, the so-called drug-induced LQTS (diLQTS). As the prolongation of the QT interval is associated with an increased risk of arrhythmic events, it has to be detected accurately also in out-of-hospital settings.

A major problem became evident 30 years ago with the publication of the report linking a therapeutic dose of the anti-histaminic drug terfenadine to the occurrence of a life-threatening arrhythmia, Torsades-de-Pointes (TdP) ventricular tachycardia [1]. This started the era of public knowledge of diLQTS [2].

It became progressively evident that a number of individuals may have a “reduced repolarization reserve” [3], a term which indicates an impairment of the physiologic redundancy in repolarizing currents. This phenomenon exposes them to a high risk for life-threatening arrhythmias whenever they are treated with I kr-blocking drugs. A major cause for this condition is represented by mutations in genes controlling the main potassium currents I kr and I k1 [4]. We had provided the first evidence for this possibility 18 years ago [4] and have recently quantified this phenomenon in the largest study ever made on subjects with diLQTS demonstrating that 30% of them carry a LQTS-causing mutation [5]. Recent data [6] suggest that a number of common genetic variants, each with a modest effect, could have a cumulative effect, facilitate drug-induced QT prolongation and help predicting the possible occurrence of TdP, in other words “predicting the unpredictable” [7,8].

diLQTS represents a major public issue because drugs which block the I kr current are prescribed every day for a variety of non-life-
threatening medical conditions and because of the impact on the medical industry which has often to withdraw effective drugs because of a few lethal events.

The glaring practical question is how to identify in advance, or very early on, the subjects at risk of developing TdP when they are treated with drugs having an I$_{Na}$ blocking effect. There is an unmet need for a simple way to know whether or not a given medication produces excessive QT interval prolongation in a specific patient. Indeed, one of the recommendations made in a recent review article on how to identify the subjects at risk of diLQTS was to use wearable QT monitors [8]. We have tackled this issue by using one such monitor, the BodyGuardian™ (BG - Preventice Solutions Group, Eagan, MN, USA).

One of the most useful tools for diagnosis, risk stratification and follow-up of LQTS patients is the 24-h 12 lead ECG Holter monitoring [9] and it is logical to compare measurements made manually by cardiologists with specific expertise in LQTS to those made by BG. Accordingly, in the present study, we have simultaneously recorded 24-h 12 lead ECG Holter together with BG and compared our manual measurements made on the Holter recordings to those made by the device. The expectation being that, if the detection of QT prolongation by the ECG patches is comparable to that obtained during Holter recordings in healthy controls and in LQTS patients, this would apply also when the QT interval is prolonged by drugs.

2. Methods

2.1. Study population and clinical assessment

Two groups of subjects were prospectively enrolled at our Center: 25 patients affected by LQTS (all genotype positive) and 20 healthy controls. The inclusion criteria were: age > 18 years; clinical stability; possibility to apply properly the BG device; to use smartphones and to give a feedback on the use of the BG; availability of internet connection in the subjects’ living place; good quality of the traces recorded. The exclusion criteria were: skin allergy or hypersensitivity to acrylic scotch tape, electrolytic gel and silicone; pregnancy.

All enrolled subjects had a 24-h standard 12 lead ECG Holter monitoring and simultaneous monitoring with BG. The ECG Holter monitoring used for this purpose was a standard 12 lead device Mortara HScribe, routinely used to assess LQTS patients followed in our Center. The interpretation of the results of the test was processed by a standard software; QT intervals were manually measured and QTc (QT interval corrected for heart rate) and the same beat with the same RR for the comparison. Each measured QTc (QTc MM) in Lead II was plotted against each difference between the BG measurements of QTc and the manually measured QTc (QTc BGM). The mean, standard deviation (SD), standard error (SE) and 95% confidence interval of each plot were calculated. High values indicate large differences between manual and BG measurements. The mean, SD, SE, minimum and maximum values and percentiles of QTc were calculated for both manual and BG measurements. The percentage of manual and BG measurements that differed >15, 20, 30, 45 ms for QTc have also been calculated. The interpretation of the results of Bland–Altman plot is not based on a statistical test for significance and thereby an a priori acceptable difference should be defined. In our case a value of ±5 ms (quite conservative) or ±10 ms (reasonably conservative) were considered as very acceptable from a clinical perspective. Comparisons were made for all subjects and also in the 2 subgroups of controls and LQTS patients. A QTc automatically measured by BG >470 ms when the QTc manually measured was ≤440 ms was considered as a false negative measurement. A QTc automatically measured by BG <440 ms when the QTc manually measured was >470 ms was defined as a false negative measurement. For a patient to be considered as misclassified, i.e. to be a true false positive or false negative, he/she should have had >20% of incorrect measurements.

2.2. Statistical analysis

A comparison between the manual measurements and the automatic QT measurements was performed with the Bland–Altman plot [10] according to the Krouwer adapted method. Each measured QTc (QTc MM) in Lead II was plotted against each difference between the BG measurements of QTc and the manually measured QTc (QTc BGM). The mean, standard deviation (SD), standard error (SE) and 95% confidence interval of each plot were calculated. High values indicate large differences between manual and BG measurements. The mean, SD, SE, minimum and maximum values and percentiles of QTc were calculated for both manual and BG measurements. The percentage of manual and BG measurements that differed >15, 20, 30, 45 ms for QTc have also been calculated. The interpretation of the results of Bland–Altman plot is not based on a statistical test for significance and thereby an a priori acceptable difference should be defined. In our case a value of ±5 ms (quite conservative) or ±10 ms (reasonably conservative) were considered as very acceptable from a clinical perspective. Comparisons were made for all subjects and also in the 2 subgroups of controls and LQTS patients. A QTc automatically measured by BG >470 ms when the QTc manually measured was ≤440 ms was considered as a false positive measurement. A QTc automatically measured by BG <440 ms when the QTc manually measured was >470 ms was defined as a false negative measurement. For a patient to be considered as misclassified, i.e. to be a true false positive or false negative, he/she should have had >20% of incorrect measurements.

3. Results

3.1. Overall population

The final study population consisted of 20 LQTS patients and 16 controls, all Caucasian, for a total of 351 measurements (219 and 132

![Fig. 1. Cartoon illustrating the way BodyGuardian Remote Monitoring System operates.](image)
respectively). Mean age was 40 ± 11 years (range 18–61). There were 15 males (40%). Among the 20 LQTS patients, there were 9 males (45%), mean age was 38 ± 13 years (range 18–61); 11 (55%) were LQT1 and 9 (45%) were LQT2, all were on beta-blocker therapy with either propranolol or nadolol. All patients signed a written informed consent. The study was approved by the local Ethics committee.

The average number of measurements per patient was 9.75, the range was between a minimum of 5 (in only 3 patients) and a maximum of 15.

Table 1 summarizes the analysis of the Bland-Altman plot and Suppl. Table 1 the descriptive statistics for the entire population included in the study. The QTc automatically measured by BG was 445 ± 47 ms, and the QTc manually measured was 446 ± 41 ms (Suppl. Table 1). The mean and SE of the Bland-Altman plot was −1.4 ± 1.8 ms in all subjects (Table 1, Fig. 2). The disagreement between BG and manual measurement was <15 ms in 57% cases, 34% of measurements had a disagreement >20 ms. (Suppl. Table 2).

All the patients were very comfortable with the dimensions of the device, especially compared to the 12 lead Holter monitoring. They did not complain of any allergy to the strip. Only three subjects complained about the alarm by the mobile phone saying that it was too noisy during the night, as the mobile phone alerts when the quality trace recording is not good.

### 3.2. Control group

Table 1 summarizes the analysis of the Bland-Altman plot and Suppl. Table 1 the descriptive statistics for the control group. The QTc automatically measured by BG was 414 ± 39 ms, and the QTc manually measured was 406 ± 26 ms (Suppl. Table 1). The mean and SE of the Bland-Altman plot was −1.4 ± 1.8 ms in all subjects (Table 1, Fig. 2). The disagreement between BG and manual measurement was <15 ms in 57% cases, 34% of measurements had a disagreement >20 ms. (Suppl. Table 2).

### 3.3. LQTS patients

Table 1 summarizes the analysis of the Bland-Altman plot and Suppl. Table 1 the descriptive statistics for the LQTS group. The QTc

<table>
<thead>
<tr>
<th>Overall population</th>
<th>N</th>
<th>351</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>−1.4</td>
<td></td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>−5.0 to 2.2</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>34.1</td>
<td></td>
</tr>
<tr>
<td>Standard error</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control group</th>
<th>N</th>
<th>132</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>3.7 to 13.0</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>26.9</td>
<td></td>
</tr>
<tr>
<td>Standard error</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LQTS patients</th>
<th>N</th>
<th>219</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>−7.2</td>
<td></td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>−12.1 to −2.4</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>−4.0</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>36.6</td>
<td></td>
</tr>
<tr>
<td>Standard error</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

Comparison between the manual measurements (MM) and the automatic QT measurements (BGM) performed with the Bland-Altman plot. Each measured QTc (QTc MM) in lead II was plotted against each difference between the BG and the manual measurements (QTc BGM – QTc MM). The mean, standard deviation, standard error and 95% confidence interval of each plot were calculated. High values indicate large differences between manual and BG measurements. LQTS: Long QT Syndrome.
automatically measured by BG was 463 ± 43 ms, the QTc manually measured was 470 ± 26 ms (Suppl. Table 1). The mean and SE of the Bland-Altman plot was −7.2 ± 2.5 (Table 1, Fig. 4). The disagreement between BG and manual measurement was <15 ms in 54% cases, 37% of measurements had a disagreement >20 ms. (Suppl. Table 2).

Fig. 3. Dots represent each manually measured QTc in lead II (QTc MM) plotted against each difference between the automated measurements of QTc by BodyGuardian™ (BGM) and the manually measured QTc (QTc BGM – QTc MM). The vertical red line indicates the upper normal QTc. The mean value of the plot is close to 0, indicating a high agreement between measurements.

Fig. 4. Dots represent each manually measured QTc in lead II (QTc MM) plotted against each difference between the automated measurements of QTc by BodyGuardian™ (BGM) and the manually measured QTc (QTc BGM – QTc MM). The vertical red line indicates the upper normal QTc. The mean value of the plot is close to 0, indicating a high agreement between measurements.
3.4. False positive and negative measurements

An incorrect measurement was observed in 9 patients but the total number of incorrect measurements was 13 out of a total of 351 measurements (3.7%). Overall, there was only one patient with >20% of erroneous measurements which might have been potentially misleading, thus indicating that a misclassification occurred in just 1 of 36 subjects (Suppl. Table 3). The subsequent review of the ECG of this patient showed that in lead II the T wave was diphasic.

The percentage of false positive measurements in the control group was 2% (3/132), in three different subjects (Suppl. Table 4A). The percentage of false negative measurements in the LQTS group was 4% (10/219) in six different patients (Suppl. Table 4B); of these 10 measurements, 4 occurred in one patient and the remaining 6 were observed in 5 patients. According to the automatic BG measurements, all the control subjects were correctly classified as not affected and all the LQTS patients as affected, with the exception mentioned above.

One automatic QTc measurement by BG in a LQTS patient was grossly wrong (214 ms) but we have chosen to report it as well, for transparency. The corresponding MM was 464 ms. As we have chosen as false negative criteria BG QTc <440 ms when MM QTc >470 ms, this measurement error is not listed among the false negative. However, this outlier was the only incorrect value among 15 measurements in the same patient and had no impact on the correct classification of the patient as affected.

4. Discussion

The present study shows that the wearable monitor BG can reliably assess the QT interval independently of whether it is normal, as in healthy controls, or prolonged as in patients affected by the congenital LQTS. This should imply that it would also be possible to remotely assess whether a patient treated with an Ia blocker manifests a prolongation of the QT interval that could predispose to TdP ventricular tachycardia.

4.1. The clinical problem

A considerable number of drugs, potentially useful for the majority of patients, has been withdrawn from the market or has never entered it because of the fear that in a few patients susceptible to Ia block they might induce life-threatening arrhythmias [11,12]. Others, still on the market, are used in a limited way because of these concerns and patients are often treated either with less effective drugs or with others that produce significant and troubling side-effects but without the risk for life-threatening arrhythmias. The evidence that genetic predisposition plays a major role in drug-induced TdP [5,6] has further contributed to the concern by most physicians that the risk for TdP cannot be predicted and that therefore Ia blockers should simply be avoided. This is wrong for two major reasons. One is that there are several drugs, rather unique for their efficacy in specific conditions, which should remain available for the vast majority of patients. The other is provided by the present study and is represented by the fact that by remotely monitoring the QT interval during the initial week or weeks of therapy - it is possible to rapidly identify the subjects at risk and to immediately withdraw the offending drug.

4.2. The present findings

The present study shows that the QTc measurement by BG is very similar to the manual measurement. Overall, the mean of the Bland-Altman plot was extremely close to zero with a small standard error (−1.4 ± 1.8 ms), which means that the differences between the two methods are not clinically important and that the two methods may be used interchangeably. Also considering the two different groups of subjects in the study, the Bland-Altman plots showed a good agreement between the two methods (8.3 ± 2.3 in the control group and −7.2 ± 2.5 in the LQTS group). The disagreement was similar for the LQTS and the control groups, as respectively 37% and 30% of the measurements disagreed by >20 ms. However, these disagreements had a minimal impact because, with just one exception, they occurred in only a fraction of the measurements of each individual while most were correct. The practically important consequence was that only 1 in 36 subjects would have been misclassified. The presence of diphasic T waves in the lead II of this patient suggests that the initial return toward the baseline has likely misled the BG device suggesting a premature return to baseline of the T wave. However, the clinician can remotely access the server and visualize the ECG trace recording on real-time. This allows the recognition of any new repolarization abnormality that may occur during the recording.

4.3. Implications

The present results are rather straightforward. They indicate that it has become possible, with the remote monitoring system just described, to follow the QT interval of a patient not only during baseline conditions but also, in all probability, during the first week or weeks of a therapy with a drug that has the potential of producing – in a minority of genetically predisposed individuals – an arrhythmogenic QTc lengthening. As this methodology appears adequate to provide reliable measurements in individuals with both a normal and a congenitally prolonged QT interval, it seems reasonable to assume that the same reliability will be preserved when the QT interval will prolong in response to certain drugs. The system has also the great advantage to allow a remote real-time visualization of the ECG traces, thus allowing to look for repolarization abnormalities. We describe three specific examples of situations where such a control would be very useful and provide much needed safety.

Among antidepressant and antipsychotic drugs of similar clinical efficacy, there are many that block the Ia current and which, therefore, are potentially dangerous for patients with a reduced repolarization reserve [3]. For example, the Ia blocking activity of olanzapine – an antipsychotic that does not prolong the QT interval but which is associated with a significant weight increase – is greatly lower than that of risperidone and ziprasidone [13]. Many psychiatrists prefer to use olanzapine instead of the other two drugs because, despite their knowledge of the detrimental effects of induced obesity, they are more concerned with the possibility of their treatment causing TdP.

The current management of asymptomatic patients affected by the Brugada syndrome and showing a type 1 ECG pattern includes the use of quinidine as prophylactic treatment [14]. The same goes for some survivors of idiopathic ventricular fibrillation [14]. However, despite encouraging supportive data [15–17], this practice is limited by the reasonable concern based on the established knowledge that quinidine – a potent Ia blocker – is not infrequently associated with QT prolongation and propensity for TdP.

Last, but not least, there is the major issue of new drugs with some degree of Ia blocking activity ready to enter the market or that have already entered the market. Just a modest QTc increase in some healthy volunteers or a few cases of TdP would block their development or cause their withdrawal. This would have two major negative consequences: huge financial losses for the companies and the loss of effective and useful drugs that could benefit many patients.

In all these 3 scenarios, the possibility of administering these drugs while remotely monitoring the QTc for 5–7 days, or longer if necessary, could help to identify on one hand the few subjects at risk and interrupt a therapy that might become dangerous and, on the other, the large number of patients who could be treated with an effective medication without significant concerns.

Conflict of interest

Peter J. Schwartz served as consultant for Preventice, Inc.; the other Authors have no conflict of interest to disclose.
Acknowledgments

The Authors are grateful to Margherita Calcagnino, MD, for her involvement in the early phase of the project, and to Pinuccia De Tomasi, BS, for expert editorial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.03.097.

References