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CLINICAL RESEARCH

Fast, accurate and easy-to-teach QT interval assessment: The triplicate concatenation method

Nouvel outil rapide, précis et facile à enseigner de mesure du QT par concaténation d'ECG tripliqués

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KEYWORDS
QT interval measurement;
Method validation;
Semiautomated measurement;
Education

Summary
Background. — The gold standard method for assessing the QTcF (QT corrected for heart rate by Fridericia's cube root formula) interval is the ''QTcF semiautomated triplicate averaging method'' (TAM), which consists of measuring three QTcF values semiautomatically, for each 10-second sequence of a triplicate electrocardiogram set, and averaging them to get a global and unique QTcF value. Thus, TAM is time consuming. We have developed a new method, namely the ''QTcF semiautomated triplicate concatenation method'' (TCM), which consists of

Abbreviations: QTcF, QT corrected for heart rate by Fridericia's cube root formula; SD, standard deviation; TAM, triplicate averaging method; TCM, triplicate concatenation method.

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concatenating the three 10-second sequences of the triplicate electrocardiogram set as if they were a single 30-second electrocardiogram, and measuring QTcF only once for the triplicate electrocardiogram set.
Aim. — To compare the TCM method with the TAM method.
Methods. — Fifty triplicate electrocardiograms were read twice by an expert and a student using both methods (TAM and TCM). We plotted Bland—Altman plots to assess agreement between the two methods, and to compare the student and expert results. The time needed to read a set of 20 consecutive triplicate electrocardiograms was measured.
Results. — Limits of agreement between TAM and TCM ranged from −8.25 to 6.75 ms with the expert reader. TCM was twice as fast as TAM (17.38 versus 34.28 min for 20 consecutive triplicate electrocardiograms). Bland—Altman plots comparing student and expert results showed limits of agreement ranging from −4.34 to 11.75 ms for TAM, and −1.2 to 8.0 ms for TCM.
Conclusions. — TAM and TCM show good agreement for QT measurement. TCM is less time consuming than TAM. After a learning session, an inexperienced reader can measure the QT interval accurately with both methods.

MOTS CLÉS
Mesure de l'intervalle QT ;
Validation de méthode ;
Mesure semi-automatique ;
Pédagogie

Résumé
Context. — La méthode de référence de mesure de l'intervalle QT est la « QT/QTcF semi-automated triplicate averaging method » (TAM). Elle consiste à mesurer semi-automatiquement 3 valeurs de QTcF issues de chacun des enregistrements électrocardiographiques (ECG) de 10 secondes enregistrés en triplicata, puis à en faire la moyenne afin d'obtenir une valeur unique de QTcF. Cette méthode est chronophage. Nous avons développé une méthode récente —la « QT/QTcF semi-automated triplicate concatenation method » (TCM), consistant en concaténer les 3 séquences de 10 secondes de l'ECG acquis en triplicata comme s'il s'agissait d'un seul ECG de 30 secondes, puis à mesurer une seule fois le QTcF.
Objectif. — Nous avons comparé la méthode TCM à la méthode TAM.
Méthodes. — 50 ECG tripliqués ont été lus par un expert et un étudiant, en utilisant les 2 méthodes (TAM et TCM). Une analyse de Bland-Altman a été réalisée afin d'évaluer la concordance de ces méthodes, et celles des mesures d'un expert comparé à un étudiant. Le temps nécessaire pour mesurer 20 ECG tripliqués a été mesuré.
Résultats. — Pour l'expert, les limites d'agrément à 95 % entre TAM et TCM s'étendent de −8,25 à 6,75 ms. Entre l'étudiant et l'expert, les limites d'agrément sont de −4,34 à 11,75 ms avec la TAM, et de −1,2 à 8,0 ms avec la TCM. La TCM est deux fois plus rapide que la TAM.
Conclusions. — Les méthodes TAM et TCM sont concordantes pour la mesure du QT, la méthode TCM étant cependant plus rapide que la méthode TAM. Après apprentissage, un étudiant est capable de mesurer le QT précisément avec chacune de ces méthodes.

Background

QT interval prolongation is a biomarker of the risk of torsades de pointes, whether drug-induced or not [1,2]. Assessing the effects of new chemical entities on QT/QTc interval duration has been a mandatory regulatory requirement during drug development since 2005 [3]. A positive signal (i.e. QT liability) of this so-called thorough QT study is considered when the upper bound of the 95% one-sided confidence interval for the largest placebo-controlled time-matched mean effect of the drug on the QTc interval is at least 10 ms compared with placebo.

The current standard for measurement of QTcF (QT corrected for heart rate by Fridericia's cube root formula) is the ''QT/QTcF semiautomated triplicate averaging method'' (TAM). Three QTcF values are determined semiautomatically from a triplicate electrocardiogram set, using a superimposed median beat. These three QTcF values, each computed from a 10-second electrocardiogram, are then averaged [4—7]. Therefore, QTcF has to be measured three times, and this method makes thorough QT studies time consuming and expensive.

The aim of this study was to validate a new method of QTcF measurement that we have named the ''QT/QTcF semiautomated triplicate concatenation method'' (TCM). This method consists of concatenating the three 10-second sequences of the triplicate electrocardiogram set as if it were a single 30-second electrocardiogram, and then

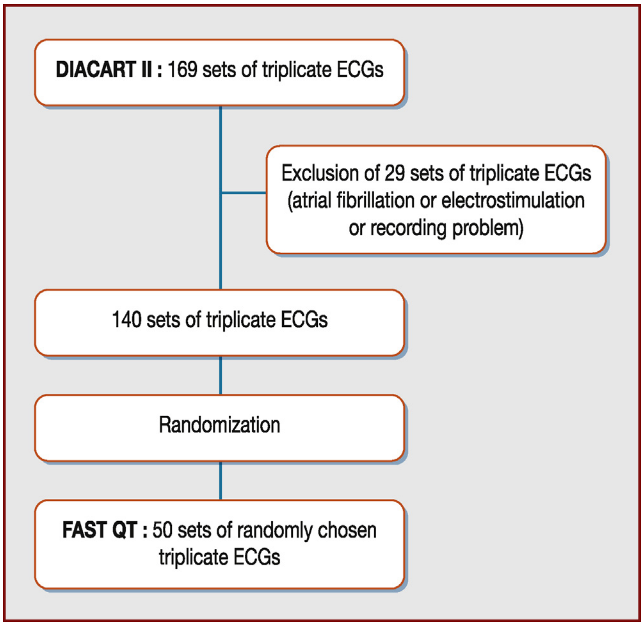

Figure 1. Flow-chart depicting selection of 50 sets of triplicate electrocardiograms (ECGs).

processing as above (semiautomated QTcF determination using a unique superimposed median beat). Thus, QTcF is measured only once for the entire triplicate set.

Our main objective was to assess agreement between the two methods. A secondary objective was to compare the time required to measure QTcF with both methods. Finally, we assessed whether a medical student [8] learning how to measure QT interval could reproduce the results of an expert.

Methods

Participants

This study consisted of an analysis of 50 triplicate electrocardiograms from DIACART II, a monocentric study conducted at Pitié-Salpêtrière Hospital Centre d'Investigation Clinique, from 2014 to 2016 (NCT02431234) [9]. One hundred and sixty-nine subjects were enrolled, and each subject had one triplicate set of 12-lead 10-second resting electrocardiograms, separated by 2-minute intervals at inclusion. A collection of 169 triplicate (507) electrocardiograms was thus initially performed. Electrocardiograms with atrial fibrillation, electrostimulation or technical recording issues were excluded, and 50 triplicate (150) electrocardiograms were randomly selected for this study (Fig. 1). Of note, patients with bundle branch block were not excluded from analysis ($n = 7$).

Ethical considerations

All subjects gave written informed consent during the initial study (DIACART II), and agreed to let their electrocardiograms be used for this ancillary study. The protocol was approved by institutional review boards and the local ethics committee.

Electrocardiogram analysis

Fifty sets of 12-lead 10-second resting triplicate electrocardiograms were analyzed for this study. Electrocardiograms were recorded using a digital electrocardiograph (ELI 280, V1.02.01; Mortara Instrument, Inc., Milwaukee, WI, USA) by trained nurses, with a sampling rate of 1000 Hz and a filter of 150 Hz.

Two semiautomated computer-assisted methods of QTcF measurement were compared: TAM, currently considered the ''gold standard''; and TCM, the new method to be validated.

A triplicate electrocardiogram was made up of three separate 10-second electrocardiogram recordings. The software used for both semiautomated measurements was CalECG, V3.7.0 (AMPS LLC, New York, NY, USA).

Description of TAM and TCM

CalECG software allows one electrocardiogram to be loaded at a time with the TAM approach, and three electrocardiograms simultaneously with the TCM approach. With TAM, QT has to be measured three times (each 10-second sequence of the triplicate electrocardiogram set must be loaded separately). The measured QT on each electrocardiogram is corrected for heart rate using Fridericia's formula ($QTcF = QT/RR^{1/3}$), and the three QTcF values are averaged to get a single QTcF value. TCM simplifies the task of QT measurement as only a single QT interval has to be measured. With TCM, the three 10-second recordings of the triplicate electrocardiogram set are loaded at the same time, and are concatenated as if they were a single 30-second electrocardiogram. The last beat of the first and second electrocardiograms and the first beat of the second and third electrocardiograms are excluded, a priori, to prevent artefacts generated on the concatenation point. However, both methods operate in the same way: once the sequence(s) is (are) loaded, representative beats are generated, the QT interval is measured semiautomatically by using the superimposed median beat and the QTcF value is obtained (Fig. 2).

Representative beats

A representative beat is generated automatically for each of the 12 leads from the detected sinus rhythm beats. In each lead, sinus rhythm electrocardiogram beats are aligned on the R-wave peak, and the representative beat is computed by averaging (computing the median value) the beats of each lead, resulting in a unique signal (representative beat) for each lead. Thus, a representative beat is not a truly recorded electrocardiogram beat, but an average of all the recorded beats in all leads. The user can manually correct the beats to be used for the computation of representative beats in case of misdetection or misclassification of sinus rhythm beats. The final outcome is 12 representative beats, one per lead.

Superimposed median beat

By superimposing the 12 single-lead representative beats, a superimposed median beat is obtained (Fig. 3). The superimposed median beat is best defined by a vector magnitude representing the set of all representative beats. The vector magnitude is computed using the square root of the sum of all squares' representative beats. The vector magnitude allows automated QT and QRS interval measurement using the threshold method. In case of erroneous placement of automatic QT/QRS fiducial marks, the user can adjust the onset/offset of the QRS complex or the offset of the T-wave. QTcF is calculated from the QT interval value using an RR value averaged from all individual sinus RR intervals.

Readers

The agreement between the two methods was examined using the measurements made by a cardiologist who is an expert in QT interval measurement (J.-E. S.) [10,11]. For pedagogic purposes, a fifth-year medical student (V. S.) with no previous experience of electrocardiogram interval measurement was trained in QT interval assessment, and his measurements were compared with those of the expert reader. The student learned TCM and TAM techniques watching the expert processing QTcF measurement (about 10 h of training).

Readers measured the 50 triplicate electrocardiogram sets four times: method 1 (TAM) and method 2 (TCM), first reading and second reading. To avoid intraobserver recall bias, each reader respected a free interval of at least 1 week between each of the four QT determinations (Fig. 2).

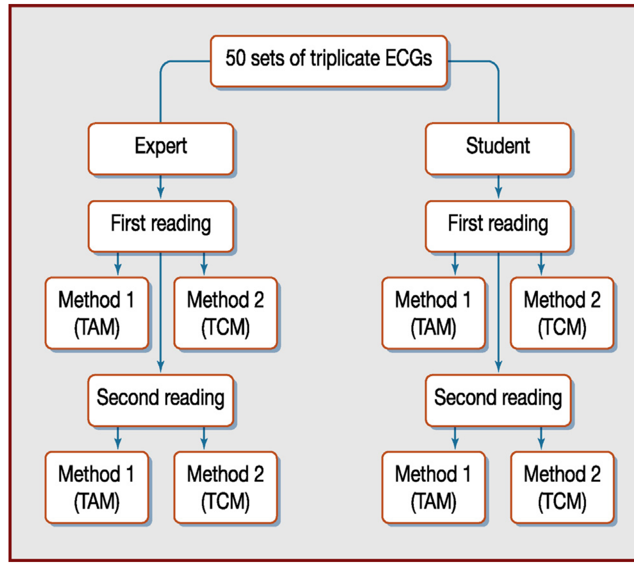

Figure 2. Flow-chart of electrocardiogram (ECG) readings: method 1 (TAM), method 2 (TCM)/first reading, second reading. TAM: triplicate averaging method; TCM: triplicate concatenation method.

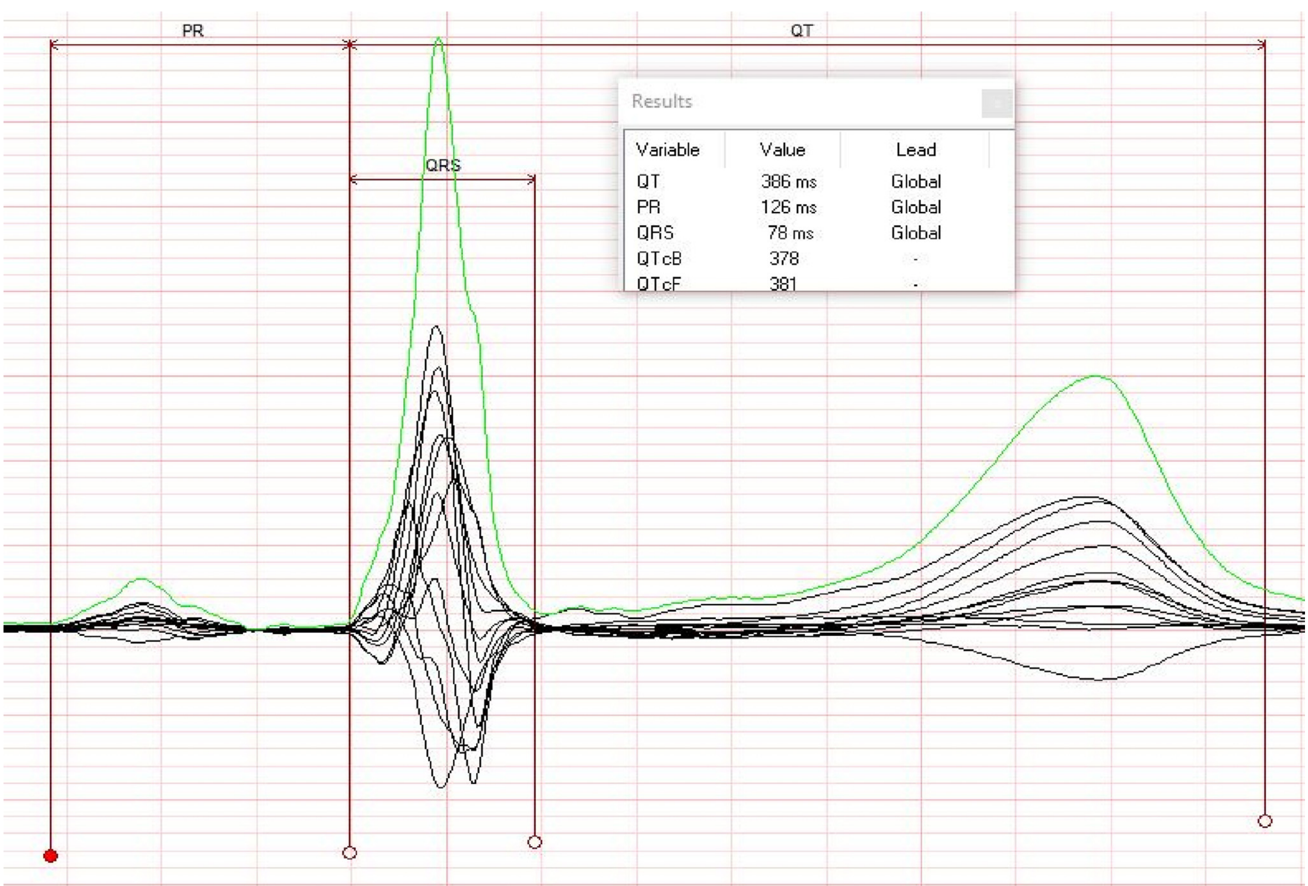

Figure 3. Superimposed median beat, with a display of vector magnitude (in green). Automatic calliper placements (PR, QRS and QT) and results (QT, PR, QRS, QTcB and QTcF), with the possibility of manual editing.

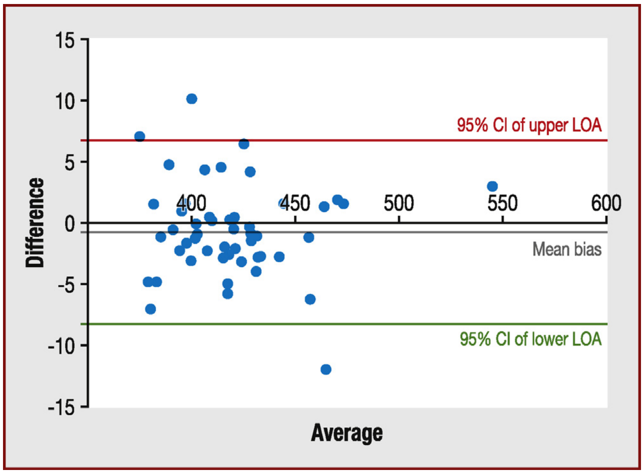

Figure 4. Bland—Altman plot: triplicate averaging method (TAM) versus triplicate concatenation method (TCM) (expert reading). CI: confidence interval; LOA: limits of agreement.

Statistical analysis

The average of the two QTcF values, obtained from the first and second readings, was considered as the global QTc value for the method. A Bland—Altman plot was constructed [12,13]. The inferior and superior limits of agreement were determined. The 95% confidence intervals for both limits of agreement were calculated. For each method (TAM and TCM), Bland—Altman plots were constructed to compare the student's measurements with those of the expert. Intrareader variability was assessed as the absolute difference (mean ± standard deviation [SD]) in QT interval measurements between the first and second reading. The association between QRS duration and degree of disagreement for assessment of QTcF duration between expert and student using TAM and TCM methods was assessed using Spearman's correlation (GraphPad, Prism 6).

Results

Agreement between TAM and TCM (expert readings)

The Bland—Altman plot showed good agreement between the TAM and TCM methods (Fig. 4). The mean ± SD bias in QTcF interval measurement was −0.75 ± 3.83 ms. The limits of agreement ranged from −8.25 to 6.75 ms (Fig. 4).

Agreement between student and expert measurements

Bland—Altman plots showed good agreement between expert and student measurements for both TAM and TCM methods (Fig. 5). With TAM, the mean ± SD bias in the QTcF interval measurement was 3.71 ± 4.10 ms, and the limits of agreement ranged from −4.34 to 11.75 ms comparing expert with student measurements. In comparison, TCM had a mean ± SD bias in the QTcF interval of 3.4 ± 2.3 ms, and the limits of agreement ranged from −1.2 to 8.0 ms comparing expert with student measurements. Agreement between student and expert measures did not differ between TAM and TCM (*P* not significant), and was not influenced by QRS duration (*P* not significant).

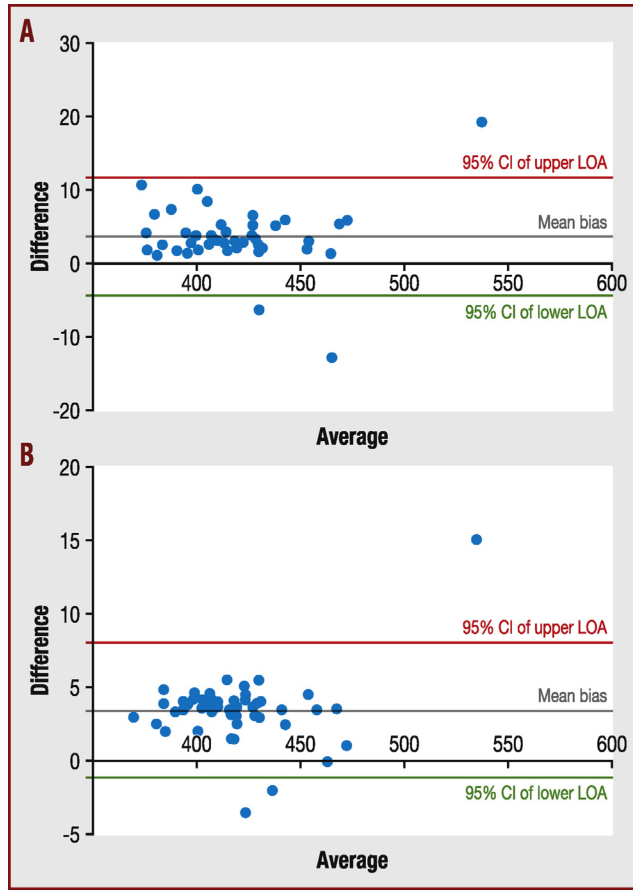

Figure 5. Bland—Altman plots. (A) Triplicate averaging method (TAM), expert versus student. (B) Triplicate concatenation method (TCM), expert versus student. CI: confidence interval; LOA: limits of agreement.

Intra- and inter-reader variability

Mean ± SD intrareader variabilities for the expert based on absolute differences for QT interval measurements were 2.58 ± 2.90 ms and 2.79 ± 3.30 ms using TAM and TCM, respectively (*P* not significant). Mean ± SD intrareader variabilities for the student were 1.33 ± 2.09 ms and 1.50 ± 2.29 ms using TAM and TCM, respectively (*P* not significant).

Time to measure QTcF

The mean time needed by the expert to measure the QT interval of 20 triplicate electrocardiogram sets was 34 min 17 s for TAM versus 17 min 23 s for TCM. Corresponding values for the student were 32 min 50 s and 19 min 43 s, respectively (Table 1).

Table 1 Time needed to measure the QT interval from 20 sets of triplicate electrocardiograms.

	First reading	Second reading	Mean
Expert			
TAM	35 min, 33 s	33 min, 00 s	34 min, 17 s
TCM	20 min, 12 s	14 min, 34 s	17 min, 23 s
Student			
TAM	36 min, 08 s	29 min, 32 s	32 min, 50 s
TCM	25 min, 13 s	14 min, 14 s	19 min, 43 s

min: minutes; s: seconds; TAM: triplicate averaging method; TCM: triplicate concatenation method.

Discussion

Our study shows that TCM yields results consistent with those of the current standard method for QTcF assessment (TAM). However, the TCM method is twice as fast as the TAM method. Intrareader expert and student variability was small, and did not differ significantly by use of the TAM or TCM method. The limits of agreement between both methods (−8.25 to 6.75 ms) did not reach the 10 ms regulatory threshold of concern for thorough QT studies.

Several methods of QT measurement have been proposed in the literature (choice of the lead, consecutive beats versus representative beat, onset of QRS complex and end of T-wave) [14,15], and this is still a matter of debate. Furthermore, it has been shown that <50% of cardiologists and <70% of physicians can measure the QT interval accurately [16]. Consequently, both accuracy and reproducibility are major points to consider when developing or teaching a new method of QT measurement.

Methods of QT measurement have evolved progressively with the development of digitized technology. Three main sources of variability of QT assessment have been identified: inter-reader variability, intrareader variability and intrinsic beat-to-beat QT variability. Triplicate electrocardiograms and median beat were introduced to reduce the intrinsic beat-to-beat variability [17,18] and electrocardiogram signal-to-noise ratio [19]. Finally, semiautomated computer-assisted methods using the generation of a superimposed median beat have shown good reproducibility in terms of intra- and inter-reader variability [20]. Despite the lack of consensus on the best way to measure the QT interval, TAM is currently the standard used by the pharmaceutical industry and the cardiology community.

When considering thorough QT/QTc studies, TAM is time consuming, and therefore expensive because, as described above, QTcF has to be measured three times. We chose to evaluate a new, faster and easy-to-teach method of QTcF measurement (TCM). Using TCM, QTcF is determined only once for the entire triplicate electrocardiogram set. Our results show good agreement between both methods. Importantly, TCM is much less time consuming than TAM. Furthermore, second readings were much faster with TCM compared with TAM, particularly for the student, arguing for a more favourable learning curve with TCM. Although the main purpose of the concatenation method is to reduce the burden of QTc computation from triplicate electrocardiograms, an indirect advantage can also be that of higher quality representative beats. Indeed, the signal-to-noise ratio of signal averaged electrocardiograms has an inverse relationship with the square root of the number of used beats, which in the presence of high noise content can lead to significantly improved waveform when going from 10-second to 30-second data segments (Supplementary Fig. 1). This new method should therefore be preferable for large sample size QT/QTc studies.

In thorough QT/QTc studies, electrocardiograms are generally read and QT intervals measured by technical staff, and an expert cardiologist validates and sometimes corrects these readings. Our results showed good agreement and similar intrareader variabilities between expert and student measurements, applying both methods, supporting the hypothesis that a trained student can accurately measure the QT interval using one or the other method. QT interval measurement can be properly assessed by non-expert readers, if they receive specific training. Thus, before extensive use of our new method in thorough QT studies, the ability of TCM to detect a subtle QTc increase of around 5 ms after moxifloxacin administration, the 'gold standard' assay sensitivity test, compared with placebo, must be confirmed.

In clinical practice, while QTc interval measurement is considered easy to perform, it remains a major daily problem, with numerous medical errors in its evaluation [16]. Many emergency and cardiology departments are not yet using digitized electrocardiogram acquisition and high-resolution triplicated QTc measurement because of expected extensive physician time consumption. This fact contributes to the dramatic imprecision found in clinical practice in QTc measurement when using a single non-digitized 10-second electrocardiogram. The time spared by TCM might help to further promote integration of digitized semiautomatic triplicated QTc measurement at the patient's bed.

Conclusions

The use of TCM for QT interval measurement is in good agreement with the use of TAM; it is twice as fast, and both methods can be learned quickly by inexperienced readers to reach performances akin to those of an expert. The ability of TCM to detect subtle QTc increases induced by moxifloxacin, the 'gold standard' assay sensitivity test, requires testing in the future before its extensive use in thorough QT studies.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.acvd.2016.12.011.

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