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

Valentin Saqué, Martino Vaglio, Christian Funck-Brentano, Maya Kilani, Olivier Bourron, Agnès Hartemann, Fabio Badilini, Joe-Elie Salem

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Running Title: Faster and accurate QT interval assessment

V. SAQUE[1], M. VAGLIO[2] (MS), C. FUNCK-BRENTANO[1] (MD-PhD), M. KILANI[1] (MD-PhD), O. BOURRON[3] (MD-PhD), A. HARTEMANN[3] (MD-PhD), F. BADILINI[2] (PhD-FACC), J.-E. SALEM[1] (MD-PhD).

1. INSERM, CIC-1421 and UMR ICAN 1166; AP-HP, Pitié-Salpêtrière Hospital, Department of Pharmacology and CIC-1421; Sorbonne Universités, UPMC Univ Paris 06, Faculty of Medicine; Institute of Cardiometabolism and Nutrition (ICAN), F-75013 Paris, France.
2. AMPS-LLC, New-York, NY, USA.
3. Service de diabétologie, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique - Hôpitaux de Paris, UPMC Univ Paris 06, Faculty of Medicine; Institute of Cardiometabolism and Nutrition (ICAN), F-75013 Paris, France.

Corresponding author : Joe-Elie Salem, joe-elie.salem@aphp.fr, Centre d'Investigation Clinique Paris-Est, Hôpital La Pitié-Salpêtrière, Bâtiment Antonin Gosset, 47-83 Bld de l'hôpital, 75651 Paris Cedex 13, Secretariat : +33 1 42 17 85 31, Fax : +33 1 42 17 85 32

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Abstract (English – 250 words)

Background: The gold standard method for assessing QTcF interval is the "QTcF semi-automated triplicate-averaging method" (TAM), consisting in measuring semi-automatically 3 QTcF values, for each 10-s sequence of a triplicate ECG set, and averaging them to get a global and unique QTcF value. Thus, TAM is time consuming. **We developed a new method** –the "QTcF semi-automated triplicate-concatenation method" (TCM), **consisting in** concatenating the three 10-seconds sequences of the triplicate ECG set as if they were a single 30-s ECG and measuring the QTcF only once for the triplicate ECGs set. We assessed the TCM method in comparison with the TAM method.

Materials-Methods: 50 triplicate ECGs were read twice by an expert and a student using both methods (TAM and TCM). We graphed Bland-Altman Plots to assess agreement between the two methods, and to compare the student and expert results. The time necessary to read a set of 20 consecutive triplicate ECG was measured.

Results: Limits of agreement between TAM and TCM ranged from –8.25 to +6.75 msec with the expert reader. TCM was twice as fast as TAM (**17.38min versus 34.28min for 20 consecutive triplicate ECG**). Bland-Altman plots comparing student and expert results showed limits of agreement of –4.34 to +11.75 ms for TAM, and of –1.2 to +8.0 ms for TCM.

Conclusion: The triplicate-averaging and triplicate-concatenation methods show good agreement for QT measurement. Triplicate-concatenation is less time consuming than triplicate-averaging. After a learning session, an inexperienced reader is able to accurately measure QT interval with both methods.

Keywords: QT interval measurement, method, agreement, semi-automated, pedagogy.

Résumé (Traduction française)

Justification: 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. Nous avons comparé la méthode TCM à la méthode TAM.

Matériels-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 msec. Entre l'étudiant et l'expert, les limites d'agrément sont de –4.34 à +11.75 msec avec la TAM, et de –1.2 à +8.0 msec avec la TCM. La TCM est deux fois plus rapide que la TAM.

Conclusion: 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.

Mots-clés: Mesure de l'intervalle QT, validation de méthode, semi-automatique, pédagogie.

Introduction

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 is a mandatory regulatory requirement during drug development since 2005 (International Conference on Harmonisation, E14 guidance). 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 to placebo.

The current standard for QTcF (QT corrected for heart rate by the cubic root Fridericia's formula) measurement is the "QT/QTcF semi-automated triplicate-averaging method" (TAM). Three QTcF values are determined semi-automatically from 3 ECG set, using a superimposed median beat. These 3 QTcF values, each computed from a 10-second ECG, are then averaged [3–6]. 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 name the "QT/QTcF semi-automated triplicate-concatenation method" (TCM). It consists in concatenating the three 10-second sequences of the triplicate ECG set as if it were a single 30-second ECG and then process as above (semi-automated 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 [7] learning how to measure QT interval could reproduce the results of an expert.

Materials & Methods

Participants

This study consisted in an analysis of 50 triplicate ECGs from DIACART II, a monocentric study conducted at Pitié-Salpêtrière Hospital - Centre d'Investigation Clinique, from 2014 to 2016 (NCT02431234) [8]. One hundred sixty nine subjects were enrolled and each subject had one triplicate set of 12-lead, 10-second resting ECGs, separated by 2-minute intervals at inclusion. A collection of 169 triplicate (507) ECGs was thus initially constituted. ECGs with atrial fibrillation, electrostimulation or technical recording issues were excluded and 50 triplicate (150) ECGs were randomly selected for the purpose of the resent 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 ECGs be used for this ancillary study. The protocol was approved by institutional review boards and the local ethic committee.

ECG analysis

50 sets of 12-lead, 10-second resting triplicate ECGs 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 semi-automated computer-assisted methods of QTcF measurement were compared:

- The TAM ("QT/QTcF semi-automated triplicate-averaging method") presently considered as the "gold standard".
- The TCM ("QT/QTcF semi-automated triplicate-concatenation method") as the new method to validate.

QTcF is the QT corrected by Fridericia's formula [QTcF=QT/RR^(1/3)] and a triplicate ECG is made of three separate 10-second ECG recordings.

The software used for both semi-automated measurements was CalECG (CalECG, V3.7.0, AMPS LLC, New-York, NY).

Description of triplicate averaging (TAM) and triplicate concatenation (TCM) methods:

CalECG software allows to load one ECG at a time with the TAM approach and three ECGs simultaneously with the TCM approach. With TAM, QT has to be measured three times (each 10-second sequence of the triplicate ECG set must be loaded separately). The measured QT on each ECG is corrected for heart-rate using Fridericia's formula and the three QTcF values are averaged to get a single QTcF value. TCM simplifies the task of QT measurement since a single QT interval has to be measured. With TCM, the three 10-second recordings of the triplicate ECG set are loaded at the same time and concatenated as if they were a single 30-s ECG. The last beat of the first and second ECGs and the first beat of the second and third ECGs are excluded *a priori* to prevent artifacts generated on the concatenation-point.

However, both methods operate in the same way: once the sequence(s) is (are) loaded, representative beats are generated, QT interval is semi-automatically measured by using the superimposed median beat and QTcF value is obtained (Fig. 2).

Representative beats: a representative beat is automatically generated for each of the 12 leads from the detected sinus rhythm beats. In each lead, sinus rhythm ECG 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 ECG beat but an average of all the recorded ones in all lead. 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 (figure 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 squared-root of the sum of all squares' representative beats. The vector magnitude allows an 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, expert in QT interval measurement (JES) [9-10]. For a pedagogic purpose, a fifth-year medical student with no previous experience of ECG interval measurements (VS) was trained to QT interval assessment and his measurements were compared to those of the expert reader. He learned TCM and TAM techniques watching the expert processing QTcF measurement (about 10 hours of training).

Readers measured the 50 triplicate ECGs set four times: method 1 (TAM) and method 2 (TCM), first reading and second reading. In order to avoid the *intra-observer recalling bias*, each reader respected a free interval of at least 1 week between each of the four QT determinations (Fig. 2)

Statistics

The average of the 2 QTcF values obtained from the first and second readings, was considered as the global QTc value for the method. A Bland-Altman plot was graphed [11,12]. The inferior and superior limits of agreement [LOA] were determined. The 95% confidence interval of both LOAs was calculated. For each method (TAM or TCM), Bland-Altman plots were graphed to compare the student measurements to those of the expert. Intra-reader variability was assessed as the absolute differences (mean ± SD) in QT interval measurements between the first and second reading. **Association between QRS duration and degree of disagreement for assessment of QTcF duration between expert and student**

using TAM and TCM methods were performed using Spearman's correlation (GraphPad, Prism 6).

Results

Agreement between TAM and TCM (expert readings)

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) msec. Limits of agreement ranged from – 8.25 to 6.75 msec (Fig. 4).

Agreement between student and expert measures

Bland-Altman plots showed good agreement between expert and student measures for both TAM and TCM methods (Fig. 5). With TAM, mean (± SD) bias in QTcF interval measurement was 3.71 ± 4.10 msec, and the limits of agreement ranged from –4.34 to 11.75 msec comparing expert to student measures. In comparison, the TCM has shown a mean (± SD) bias in QTcF interval of 3.4 ± 2.3 msec, and limits of agreement ranging from –1.2 to 8.0 msec comparing expert to student measures. Agreement between student and expert measures was not different between TAM and TCM (p=ns), **and was not influenced by QRS duration (p=ns).**

Intra- and inter-reader variability

Intra-reader variability of the expert based on absolute differences (mean ± SD) for QT interval measurements was 2.58 ± 2.90 msec and 2.79 ± 3.30 msec using TAM and TCM method, respectively (p=ns). Intra-reader variability of the student was 1.33 ± 2.09 msec and 1.50 ± 2.29 msec using TAM and TCM method, respectively (p=ns).

Time to measure QTcF

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

Discussion

Our study shows that TCM yields results consistent with those of the current standard method of QTcF assessment (TAM). The TCM method is however twice as fast as the TAM method. Intra-reader expert and student variability was small and did not significantly differ by use of the TAM or TCM method. The limits of agreement between both methods (–8.25 to 6.75 msec) did not reach the 10 msec 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 vs. representative beat, onset of QRS complex and end of T-wave) [13,14] and this is still a matter of debate. Furthermore, it has been shown that less than 50% of cardiologists and 70% of physicians are able to accurately measure the QT interval [15]. 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 progressively evolved with the development of digitized technology. Three main sources of variability of QT assessment have been identified: inter-reader variability, intra-reader variability and intrinsic beat-to-beat QT variability. Triplicate ECGs and median beat were introduced to reduce the intrinsic beat-to-beat variability [16,17] and ECG signal to noise ratio [18]. Finally, semi-automated computer-assisted methods using the generation of a superimposed median beat have shown good reproducibility in terms of intra and inter-reader variability [19]. Despite the lack of consensus on the best way to measure QT interval, the TAM method (QT/QTcF semi-automated triplicate-averaging method) currently is the standard used by pharmaceutical industry and the cardiology community.

When considering thorough QT/QTc studies, the TAM method 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 ECG set. Our results show a good agreement between both methods. Importantly, TCM is much less time consuming than TAM. **Furthermore, second readings were much faster with TCM as compared to TAM, particularly for the student, arguing for a more favorable learning curve of TCM. Although the main purpose of the concatenation method is to reduce the burden of QTc computation from triplicate ECGs, an indirect advantage can also be that of higher quality representative beats. Indeed, the signal-to-noise ratio of signal averaged ECG 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 form 10- to 30-seconds data segments (Supplementary figure 1).** This new method should therefore be preferred for large sample size QT/QTc studies.

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

In clinical practice, while QTc interval measurement is considered as easy to perform, it remains a major daily problem, with numerous medical errors in its evaluation [15]. Many emergency and cardiology departments are not yet using digitized ECG 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 while using a single non-digitized 10-sec ECG. The time spared by TCM might help to further promote integration of digitized semi-automatic triplicated QTc measurement at patient's bed.

Conclusion

The triplicate concatenation method of QT interval measurement is in good agreement with the standard triplicate averaging method. It is twice as fast and both methods can be learned quickly by inexperienced readers to reach performances akin to those of an expert. **Ability of TCM to detect subtle QTc increase induced by moxifloxacin, the 'gold standard' assay sensitivity test, is warranted in the future before its extensive use in TQT studies.**

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Figure legends

Figure 1: Flow-chart: selection of 50 sets of triplicate ECGs.

Figure 2: Flow-chart of ECG readings: method 1 (TAM) and method 2 (TCM) / 1st reading, 2nd reading. (TAM: Triplicate averaging method. TCM: triplicate concatenation method.)

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

Figure 4: Bland-Altman plot: TAM versus TCM (expert reading).

Figure 5A: Bland-Altman plot: TAM, expert versus student.

Figure 5B: Bland-Altman plot: TCM, expert versus student.

Table

Table 1: Time needed to measure QT interval from 20 sets of triplicate ECG.

	1st reading	2nd 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

Figures

Figure 1. Flow-chart: selection of 50 sets of triplicate ECGs.

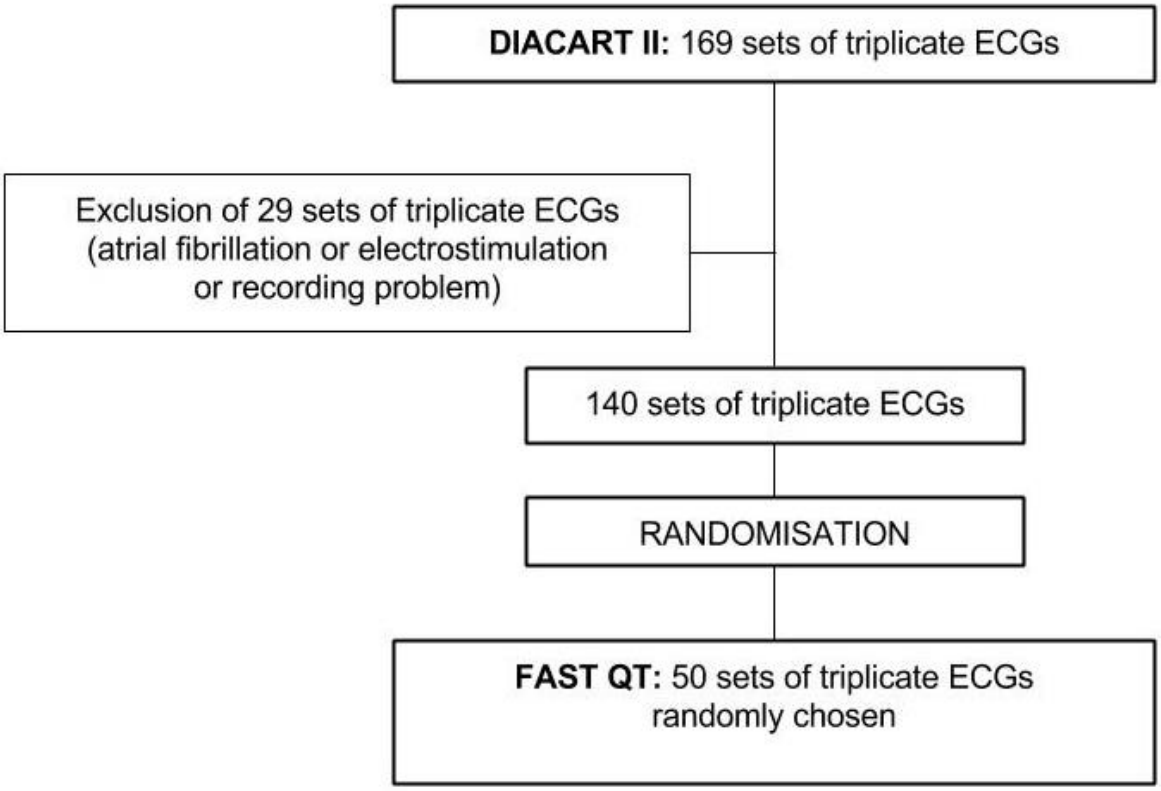
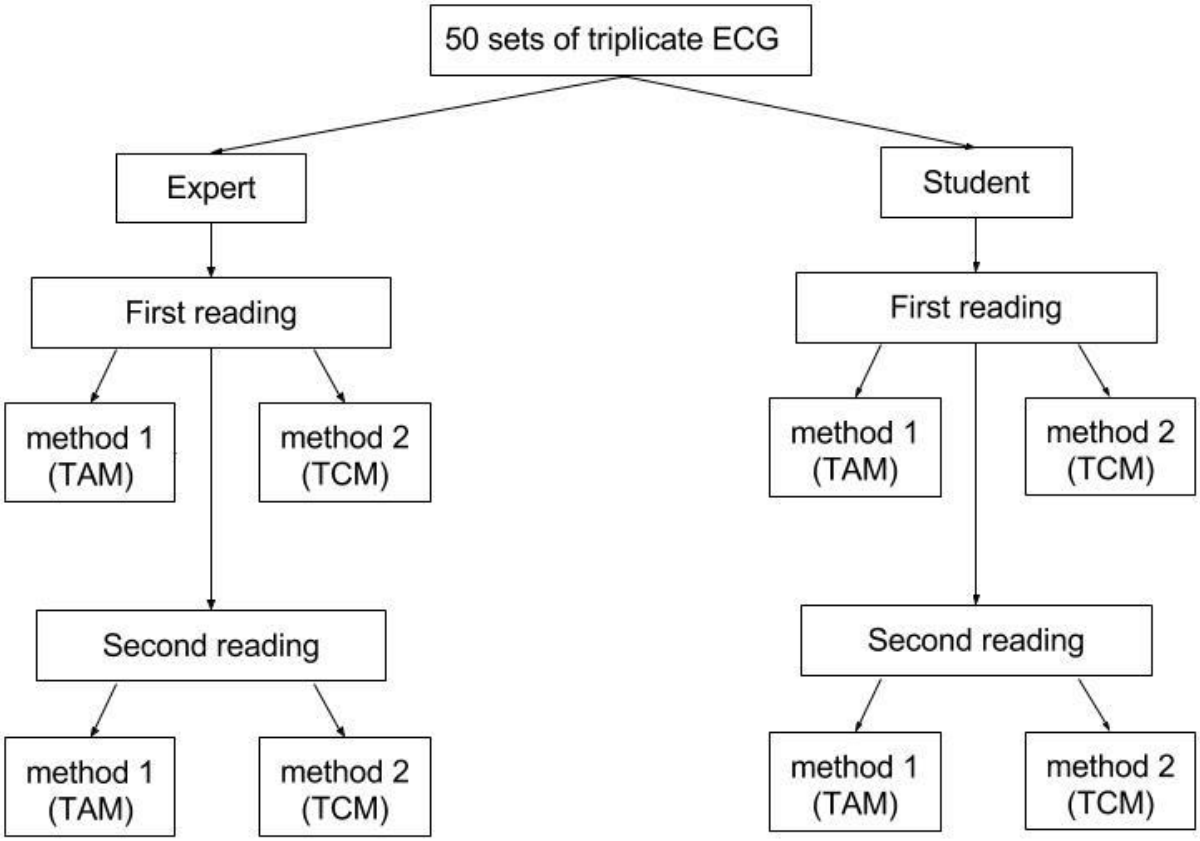


Figure 2. Flow-chart of ECG readings: method 1 (TAM) and method 2 (TCM) / 1st reading, 2nd reading. (TAM: Triplicate averaging method. TCM: triplicate concatenation method.)



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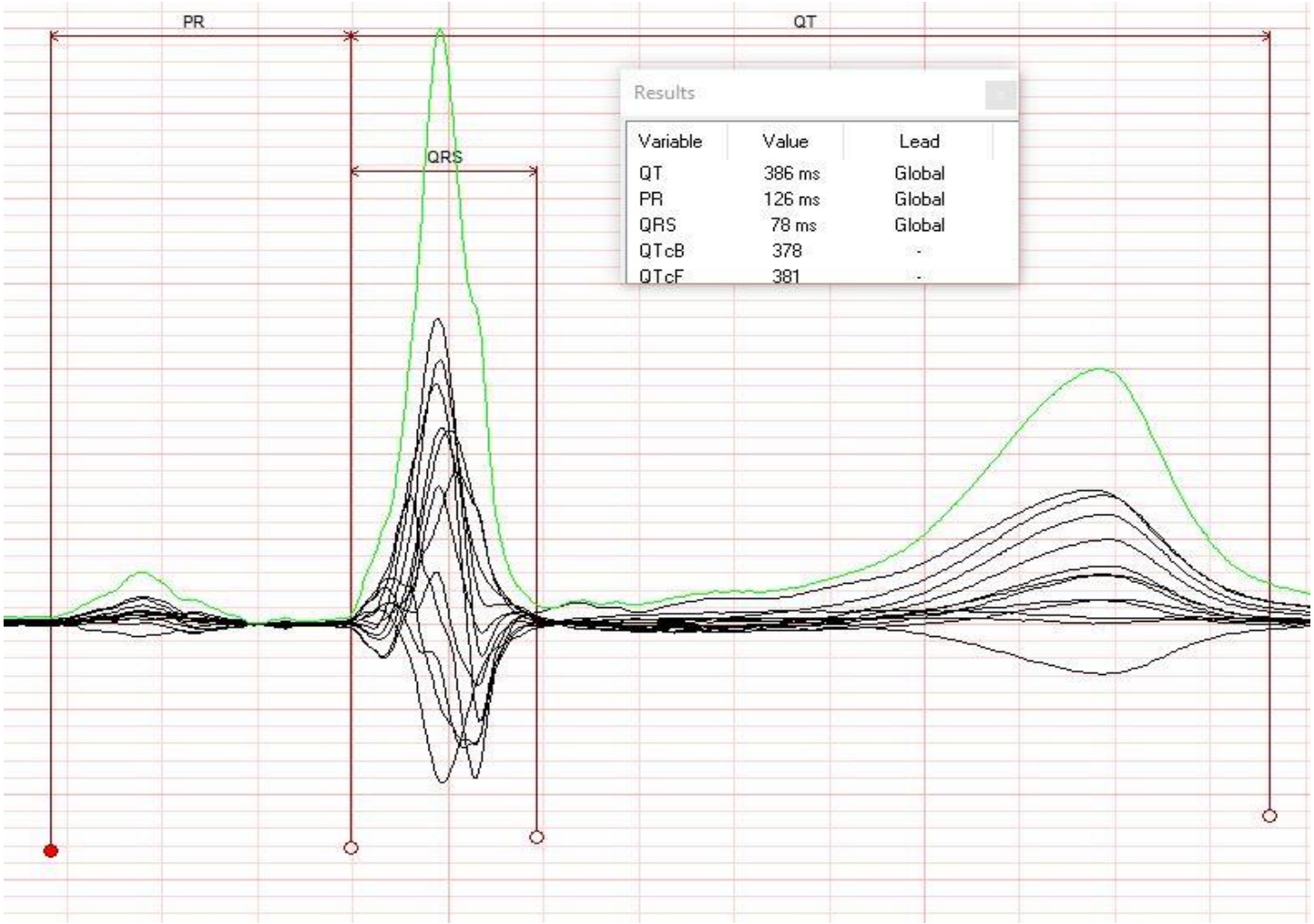

Figure 4. Bland-Altman plot: TAM versus TCM (expert reading).

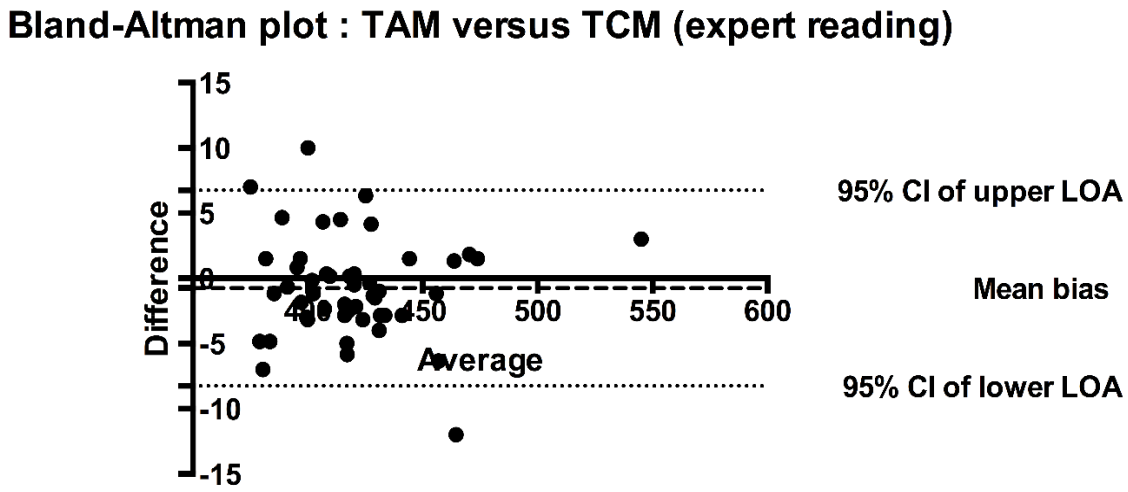

Figure 5A. Bland-Altman plot: TAM, expert versus student.

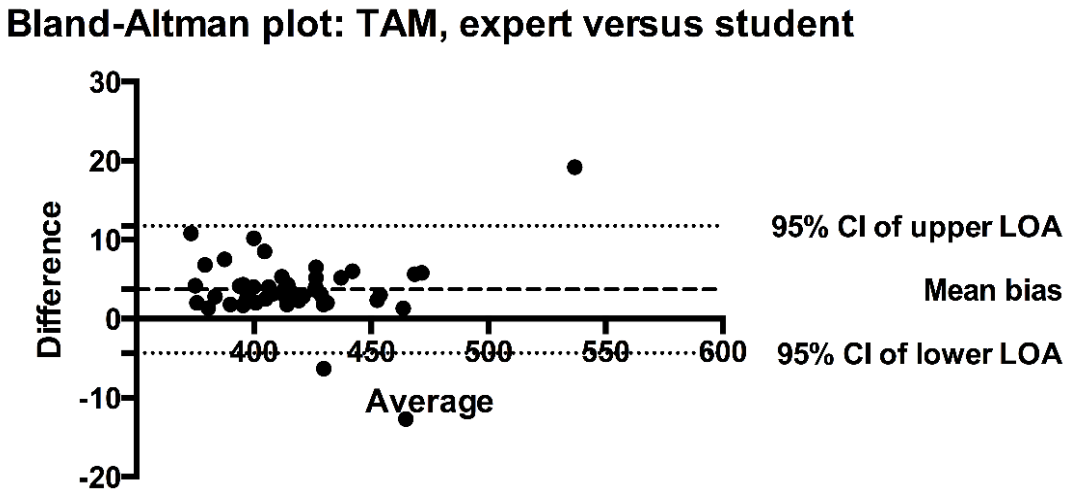

Figure 5B. Bland-Altman plot: TCM, expert versus student.