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## Original article

# Choice of an alternative lead for QT interval measurement in serial ECGs when Lead II is not suitable for analysis

Vaibhav Salvi\*, Dilip R. Karnad, Vaibhav Kerkar, Gopi Krishna Panicker, Deepak Manohar, Mili Natekar, Snehal Kothari, Dhiraj Narula, Yash Lokhandwala

Research Section, Quintiles Cardiac Safety Services, 502 A, Leela Business Park, M.V. Road, Andheri (East), Mumbai 400 059, India

## ARTICLE INFO

## Article history:

Received 20 April 2012

Received in revised form

8 May 2012

Accepted 17 July 2012

Available online 1 August 2012

## Keywords:

Cardiac safety of drugs

QT dispersion

T wave vector

Thorough QT/QTc study

Electrocardiography

## ABSTRACT

**Introduction:** Conventionally, QT interval is measured in lead II. There are no data to select an alternative lead for QT measurement when it cannot be measured in Lead II for any reason.

**Methods and results:** We retrospectively analyzed ECGs from 1906 healthy volunteers from 41 phase I studies. QT interval was measured on the median beat in all 12 leads. The mean difference in QT interval between lead aVR and in Lead II was the least, followed by aVF, V5, V6 and V4; lead aVL had maximum difference. The T wave was flat (<0.1 mV) in Lead II in 6.9% of ECGs; it was also flat in 20% of these ECGs (1.4% of all ECGs) in Leads aVR, aVF and V5.

**Conclusions:** When QT interval cannot be measured in Lead II, the best alternative leads are aVR, aVF, V5, V6 and V4 in that sequence. It differs maximally from that in Lead II in Lead aVL.

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## 1. Introduction

The QT interval is routinely measured in 12-lead ECGs to study cardiac repolarization. Prolongation of the QT interval is associated with sudden death and malignant ventricular arrhythmias including torsades de pointes and ventricular fibrillation.<sup>1</sup> Since heart disease, genetic factors, electrolyte disturbances and drugs may affect the QT interval, serial measurements of QT interval are often required in clinical practice. The QT interval is conventionally measured in lead II for various reasons.<sup>1–7</sup> Garson suggests that lead II usually shows a long single wave rather than discrete T and U waves,<sup>2</sup> making it easy to measure the QT interval. Camm and Malik

state that QT interval is usually the longest in lead II in individuals without any repolarization abnormality.<sup>4</sup> Moss et al used lead II for QT interval measurement in patients in the congenital long QT syndrome registry of the University of Rochester.<sup>6</sup> Consequently, the cut-off values for the prolonged QT interval have all been defined using QT measurements in lead II from patients with congenital long QT syndrome.<sup>6</sup>

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) requires all new drugs with systemic bioavailability to be subjected to a thorough QT/QTc (TQT) study to evaluate their effects on the QT intervals per the E14 guidance.<sup>1</sup> In these thorough QT/QTc (TQT) studies, QT

\* Corresponding author. Tel.: +91 22 6696 3872, fax: +91 22 6695 0159.

E-mail address: [vaibhav.salvi@quintiles.com](mailto:vaibhav.salvi@quintiles.com) (V. Salvi).

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<http://dx.doi.org/10.1016/j.ihj.2012.07.023>

interval in ECGs recorded at several time points after administration of a study drug or placebo are compared with pre-dose values.<sup>8–10</sup> In a recent review of 21 TQT studies, 14 studies had reported the method of QT measurement; it was measured in Lead II in 8 studies.<sup>11</sup> The ICH E14 guidance also states that “a consistent approach” should be used in choice of leads for QT measurement for the entire study. This is because the QT interval in various leads of a 12-lead ECG (QT dispersion) can differ by 40 to 60 ms in healthy individuals<sup>12</sup> and an apparent prolongation of the QT interval may be observed merely because the QT interval was measured in different leads in serial ECGs from the same subject. However, sometimes the quality of the tracing in lead II may not permit accurate interval measurement, and the QT interval may have to be measured in another lead. For example, in a TQT study evaluating the effect of Brivaracetam on the QT interval, QT interval was measured in lead II in only 35% of cases and was measured in lead V3 in 14%, Lead III in 10% Lead V4 in and lead V2 in 9%.<sup>13</sup> This raises an important question: which is the best alternative lead for QT interval measurement? An ideal alternative lead would be one in which the QT interval is closest to that measured in Lead II. As there was no published data on this question, we conducted this study in 1906 healthy volunteers where QT interval was measured in all 12 leads in order to find the best alternative to lead II.

## 2. Methods

The present study is a retrospective analysis based on ECGs from 1906 healthy normal volunteers from 41 phase I studies. All studies were approved by respective institutional review boards and used stringent screening methods to select healthy normal volunteers. ECGs were recorded using a digital electrocardiograph (Eli 250, Mortara Instrument Inc, Milwaukee, WI) with a sampling rate of 1000 Hz, speed of 25 mm/s and amplitude of 10 mm/mV and electronically transmitted to the central laboratory of Quintiles ECG Services, Mumbai, India for analysis. All ECGs were converted into an FDA compliant XML (extensible markup language) file format and the various intervals measured manually by four expert readers using digital on-screen callipers (CalECG version 2.7, AMPS LLC, NY).

The QT intervals were measured on a representative median beat in each of the twelve leads. The QT interval was measured from the onset of the first deflection of the QRS complex to the intersection of the terminal part of the T wave with the isoelectric line (the line joining midpoints of the preceding and following T-P segments). If a U wave interrupted the T wave before it returned to baseline, the QT interval was measured as the nadir between T and U waves.<sup>14–16</sup> Since there can be considerable intra-reader variability in QT interval measurement, a set of 100 ECGs were read twice by all readers to quantify intra-reader variability. The intra-reader variability for the readers ranged from 2.7 to 3.2 ms, with a mean of 3.01 ms.

We also measured the T wave amplitude in a median complex of each lead. As presence of a flat T wave (T wave amplitude <1 mm or 0.1 mV) can lead to increased measurement variability and is often used as a criterion to select another lead for QT measurement,<sup>16,17</sup> analysis was also

performed after excluding data from leads in which T wave amplitude was <±1 mm. As amplitude of the T wave depends on its axis, frontal plane T wave axis was also noted for each ECG.

### 2.1. Statistical methods

Differences between QT interval in each lead and that in Lead II were compared using the paired t test. Adjustment for multiplicity of comparisons was made using the Bonferroni correction;  $\alpha = 0.005$  was used as a cut-off for statistical significance. The actual difference in QT interval measurements in each of the 11 leads and that in Lead II (with the positive or negative sign) as well as absolute difference (i.e. without the positive or negative sign) was obtained. All eleven leads were then ranked such that the lead with the least absolute difference was ranked 1 and the lead with the maximum difference was ranked 11.

## 3. Results

The QT interval in lead II in 1906 normal healthy subjects was  $391.7 + 34.6$  ms (mean + SD). When the actual difference between each of the 11 leads and Lead II was calculated, the QT interval was shorter in leads V3, V4 and V5 than in Lead II (Table 1) and was longer than that in Lead II in the other 8 leads. However, when looking for the lead with the QT interval closest to that in Lead II, it does not matter if the difference is positive or negative, what matters is that the absolute difference should be the least. We found the least absolute difference in QT intervals in aVR followed by aVF (Table 1). Lead V1, aVL and Lead III showed the maximum difference. We found that 6.9% of ECG had flat T waves in Lead II (Table 1). Of these, the T wave amplitude was also <1 mm in lead aVR, aVF and V5 in 20% cases (1.4% of all 1906 ECGs). After excluding ECGs with flat T waves, the absolute differences were the least with aVF followed by aVR and highest in lead V1 (Table 1).

The mean T wave axis was  $32^\circ$  (SD  $23^\circ$ ) for all ECGs; it was  $34^\circ$  (SD  $21^\circ$ ,  $n = 1773$ ) for ECGs with T wave amplitude  $\geq 0.1$  mV in Lead II and  $5^\circ$  (SD  $34^\circ$ ,  $n = 133$ ) for ECGs with T wave amplitude <0.1 mV in Lead II.

As the lead with the QT interval closest to Lead II may differ from individual to individual, we ranked the 11 leads based on the absolute difference in QT interval between that lead and Lead II in the 1906 ECGs; the lead with the least absolute difference was ranked 1. Here too, the median rank was the least for lead aVR and lead aVF (Table 1). Fig. 1 shows the histograms of ranks of each of the individual 1906 ECGs. This shows that the best alternative leads are aVR, aVF, V5, V6 and V4. In 17.5% of ECGs, QT in lead aVR was closest to that in Lead II, while lead aVF was the closest in 17.4% of ECGs followed by V4 (11.4%) and V5 (10.7%).

## 4. Discussion

Our study showed that the QT interval was closest to Lead II in lead aVR followed by aVF, and the precordial leads V5, V6 and V4. The QT interval in each of the 12 leads has been reported in

**Table 1 – Difference in ms between QT intervals measured in each of the 11 leads from that in Lead II and medians and interquartile ranges of ranks of each lead of the 1906 12-lead ECG. Ranks were assigned such that the lead with the QT interval closest to that measured in Lead II (least absolute difference) was assigned Rank 1, while the one where it differed maximally was assigned Rank 11.**

Lead	All ECGs			ECGs with T wave amplitude $\geq \pm 0.1$ mV			ECGs with T amplitude $< 0.1$ mV <sup>a</sup>
	Absolute difference (ms)	Actual difference (ms)	Rank	Absolute difference (ms)	Actual difference (ms)	Rank	
	Mean (99.5% CI)	Mean (99.5% CI)	Median (IQR)	Mean (99.5% CI)	Mean (99.5% CI)	Median (IQR)	%
I	13.0** (12.1, 14.0)	7.5** (6.3, 8.7)	5 (3, 7)	11.8** (10.9, 12.7)	7.3** (6.3, 8.4)	4 (3, 6)	8.97
III	18.5** (17.3, 19.6)	10.9** (9.4, 12.5)	6 (3, 8)	15.2** (13.7, 16.8)	11.3** (9.5, 13.2)	8 (7, 9)	54.93
aVR	8.7** (8.1, 9.4)	1.0** (0.2, 1.9)	3 (2, 5)	7.9** (7.4, 8.5)	0.9* (0.1, 1.6)	3 (2, 5)	6.45
aVF	9.1** (8.4, 9.8)	3.2** (2.3, 4.1)	3 (2, 5)	7.4** (6.9, 8.0)	3.4** (2.6, 4.1)	3 (1, 5)	26.86
aVL	22.1** (20.9, 23.3)	16.6** (15.0, 18.1)	7 (4, 8)	18.4** (16.9, 19.8)	14.1** (12.3, 15.9)	10 (9, 10)	47.32
V1	24.1** (22.8, 25.5)	18.4** (16.7, 20.1)	7 (4, 9)	23.4** (21.5, 25.3)	18.3** (16.0, 20.7)	8 (6, 9)	47.11
V2	14.4** (13.4, 15.5)	2.3** (0.9, 3.7)	5 (3, 7)	12.9** (11.9, 13.9)	0.6 (–0.7, 1.9)	4 (2, 6)	7.61
V3	12.5** (11.6, 13.4)	–3.2** (–4.4, –2.0)	5 (3, 7)	11.5** (10.7, 12.2)	–3.9** (–5.0, –2.9)	4 (2, 6)	5.35
V4	11.5** (10.7, 12.3)	–2.9** (–4.1, –1.9)	4 (2, 6)	10.5** (9.8, 11.2)	–3.6** (–4.6, –2.6)	4 (2, 6)	5.04
V5	10.7** (9.8, 11.5)	–1.2* (–2.3, –0.1)	4 (2, 6)	9.6** (8.8, 10.4)	–1.5** (–2.5, –0.5)	4 (2, 5)	6.24
V6	10.9** (10.0, 11.7)	1.9** (0.9, 3.0)	4 (2, 6)	9.7** (9.0, 10.4)	1.8** (0.9, 2.7)	4 (2, 5)	9.34

Note: \*  $< 0.005$ ; \*\*  $< 0.001$ . CI: Confidence interval; IQR: Interquartile range.

a 6.9% of ECGs in Lead II had T wave amplitude  $< 0.1$  mV.

studies when QT dispersion (difference between the longest and shortest QT intervals in different leads of the same ECG) was considered a surrogate marker of dispersion of repolarization in the ventricular myocardium.<sup>18–24</sup> QT dispersion is now rarely studied as it failed to be a reliable predictor of proarrhythmia.<sup>14,25,26</sup> Macfarlane et al studied effect of age on QT dispersion in 1501 healthy normal volunteers. Although the authors did not study this aspect, data from their paper showed that the lead with mean actual QTc interval closest to that in lead II ( $390.3 \pm 18.7$  ms) was aVF ( $390.8 \pm 19.2$  ms) followed by lead V4 ( $389.9 \pm 17.9$  ms).<sup>19</sup> In the same study, the leads which had QT interval farthest from lead II were lead I ( $386.4 \pm 18.6$  ms) and lead aVL ( $386.6 \pm 19.1$  ms). Davey analyzed his QT dispersion data differently; the QT interval in lead II was correlated with QT interval in each of other 11 leads, the highest correlation coefficient ( $r = 0.81$ ) was obtained with lead aVF.<sup>22</sup> In another study, Sadanaga et al studied QT dispersion in healthy Japanese subjects and compared it with that in patients receiving psychotropic drugs. As in our study, they too found that the mean QT interval measurement closest to that in lead II ( $353 \pm 29$  ms) was observed in lead aVF ( $351 \pm 30$  ms) while lead aVL had a mean QT interval measurement farthest from lead II ( $332 \pm 31$  ms).<sup>20</sup>

Why is the QT interval in leads aVF or aVR closest to that in Lead II? It was previously thought that the difference in QT interval in various leads was due to transmural dispersion of ventricular repolarization. However, subsequent studies show that the QT interval in each lead depends on the direction of the general T wave vector,<sup>27,28</sup> projections of T wave vector loops on the 12 leads of the ECG,<sup>29,30</sup> distance between individual leads and the heart,<sup>27</sup> properties of intervening tissues<sup>27</sup> and electrical activity in the myocardium underlying the precordial leads.<sup>27</sup> The limb leads of the ECG are assumed to be attached to the angles of the hypothetical Einthoven's triangle represented by the torso with the heart at its centre (Fig. 2A). The six limb leads of the ECG are therefore oriented

in a hex-axial reference system (Fig. 2B) with Lead II having an axis of  $+60^\circ$ . The leads with their axes closest to lead II are Lead – aVR (axis  $+30^\circ$ ) on one side and lead aVF (axis  $+90^\circ$ ) on the other side. Not surprisingly, QT interval measurements in these leads were the closest to those in Lead II in our study. Schamroth recommends the use of lead aVL for QT interval measurements as the U wave is usually isoelectric in this lead, and it also has the earliest Q onset when compared to other leads.<sup>7</sup> However, we found that QT interval in Lead aVL, which has its axis perpendicular ( $-30^\circ$ ) to that of Lead II, differed maximally from that in Lead II.

One of the situations when QT interval may be measured in an alternative lead is when T wave amplitude in Lead II is  $< 0.1$  mV; this was found in 6.9% of ECGs in our study. Since T wave amplitude depends on T wave axis, it may be possible that the T wave amplitude in aVR, aVF or V5 may also be low since the axes of these leads are close to that of Lead II. However, we found that T wave amplitude was  $< 0.1$  mV in Lead II as well as all three alternative leads in only 1.4% of ECGs. Thus, it was possible to use these alternative leads in more than 98% of all ECGs.

#### 4.1. Limitations and strengths

Our study has one main limitation: a single ECG from each subject was selected for evaluation. Whether a different lead would have been superior in another ECG from the same subject is debatable. On the other hand, use of digital ECGs with high sampling rates, large number of subjects, and measurement of intervals by experienced readers in a core ECG lab are some of the strengths of our study.

## 5. Conclusion

QT interval is commonly measured in Lead II. Our study indicates that when the tracing in Lead II is of poor quality,

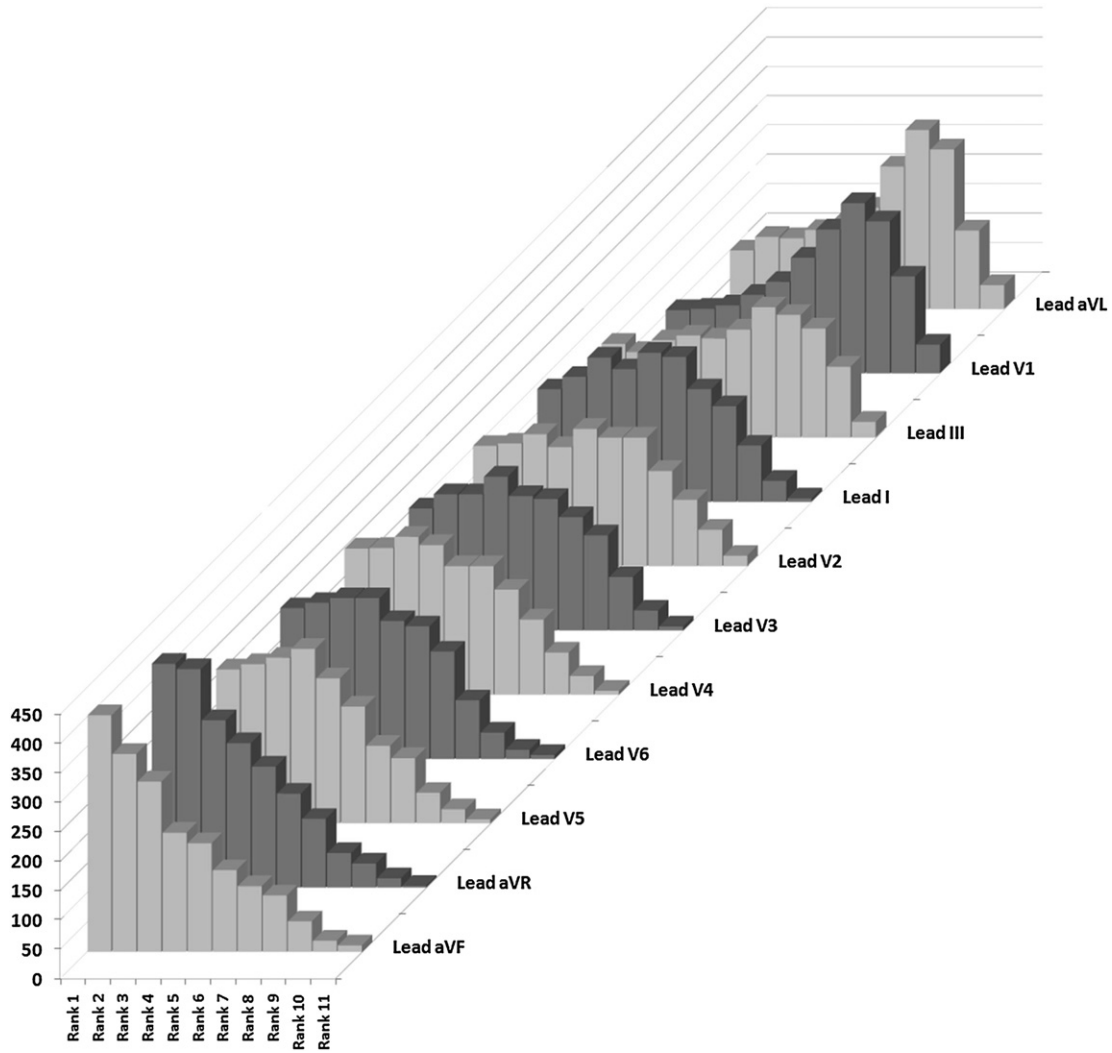


Fig. 1 – Histograms of ranks assigned to each lead of 1906 ECGs. Ranks were assigned such that the lead with the QT interval closest to that measured in Lead II was assigned Rank 1, while the one where it differed maximally was assigned Rank 11. Lead aVR had the maximum number of ECGs with Rank 1 followed by aVF. Maximum ECGs with Ranks 10 and 11 were seen in lead aVL.

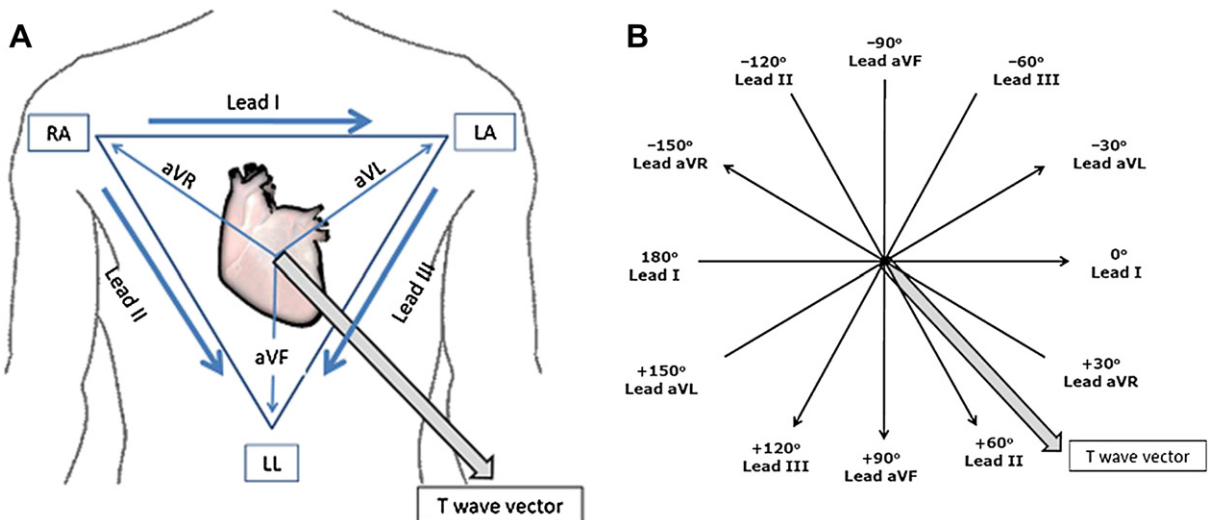


Fig. 2 – A) Position of T wave vector with respect to Einthoven’s triangle. B) Position of T wave vector with respect to hex-axial system of leads.



measuring QT interval in Lead aVR or Lead aVF would give a value closest to that in lead II. Since the QT interval in a particular lead depends on the size and shape of the T wave, which in turn is influenced largely by the direction of the global T wave vector, Leads aVR and aVF, with their axes closest to that of lead II, appear to be the best alternatives to Lead II for QT interval measurement. Our study also shows that Lead aVL should not be used for QT interval measurements when baseline evaluations are performed in lead II.

### Authors' disclosures

**Employment:** Vaibhav Salvi, Gopi Krishna Panicker, Vaibhav Kerkar, Mili Natekar and Snehal Kothari are employees of Quintiles Cardiac Safety Services, Mumbai. **Consultant or Advisory Role:** Dilip Karnad and Dhiraj Narula are Consultants to Quintiles Cardiac Safety Services. **Stock Ownership:** None. **Honoraria:** None. **Research Funding:** None. **Expert Testimony:** None. **Other Remuneration:** None.

### Conflicts of interest

All authors have none to declare.

### Acknowledgments

The authors are grateful to Dr. Hemant Bhoir for his technical assistance in the conduct of the study. We also thank Jim Chestnut for providing access to relevant literature.

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