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Review Article

QT Interval Revisited —Not Just the Matter of "Interval," but "Dynamics, Variability and Morphology" Matter!—

Tetsunori Saikawa MD*[1], Mikiko Nakagawa MD*[1], Naohiko Takahashi MD*[2]

*[1]Department of Cardiovascular Science, Faculty of Medicine, Oita University
*[2]Department of Internal Medicine I, Faculty of Medicine, Oita University

Recently, the effects of QT interval prolongation have received more attention among clinicians, industry, and official regulatory agencies. Some have advocated the total elimination or discontinuing development of drugs which prolong the QT interval. In this review, we will give a brief overview of the pathophysiology and the dynamic variability and morphology of the QT interval. From the view point of arrhythmogenesis, QT interval prolongation with increased heterogeneity of ventricular repolarization is critical. The problem is how to detect such an abnormal repolarization. To detect heterogeneity, a new index should be developed and validated, and it must incorporate QT variability and morphology of the T wave. The heart rate correction of the QT interval is also an important issue, and disclosing conflict-corrected QT intervals depend on the formulae used.

Not just QT interval prolongation is important; what also matters is the heterogeneity of ventricular repolarization.
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Key words: QT interval, Heterogeneity, Morphology, Variability

1. Introduction

The Electrocardiogram (ECG) is still one of the most important tools in the field of cardiology,[1] and is described as the "cardiologist's best friend."

Since Einthoven's invention of modern electrocardiography[2] (**Figure 1**), many types of equipment have been developed and used clinically. Electronic circuits for recording the ECG, however, are not uniform among the numerous companies marketing electrocardiographs, although there are certain rules to assure the precision and accuracy for electrocardiographs. One rule specifies that input signals should be reconstructed with no more than a 5% distortion.

From the view point of quality control and standardization, however, little endorsement is given to any electrocardiograph regarding precision and accuracy of the recorded ECG, since the recording of the ECG is not comparable among machines.

In the era of digital and global cooperation, data- or information-sharing is extremely important, whether the data are in analog or digital format. At present, however, the system which enables mutual digital data-sharing, such as digitally recorded ECGs by

Address for correspondence: Tetsunori Saikawa MD, Department of Cardiovascular Science, Faculty of Medicine, Oita University, 1-1 Idaigaoka, Hazamachyou, Yufu City, Oita 879-5593, Japan. Tel: 097-586-6037 Fax: 097-586-6050
E-mail: saikawa@med.oita-u.ac.jp

various machines, is not available. For this purpose, new systems which make the mutual sharing of data and information possible are still pending, including sharing the data of other medical wave forms. In other words, standardization of the ECG is necessary.

Recently, we developed the MFER[3] (Medical Waveform Format Encoding Rules; MFER committee http://www:mfer.org, http://www.medis.or.jp) system, which enables us not only to view, but also analyze, ECGs recorded by other digital machines if the machines have MFER-adapted output. MFER (ISO/TS11073–92001) was published very recently. This system is applicable to standard 12-lead ECG and ambulatory ECG monitoring systems. MFER is now extending its application to electroencephalography and other medical wave forms. Thus, MFER-implemented electrocardiographs will be desirable for future clinical studies, since it makes it would be possible to compare and/or analyze all ECGs within one center, or to share the data by with any center which has a MFER. This is the ultimate goal of the MFER committee.

2. QT Interval

2-1. Pathophysiology

Ventricular repolarization has long been one of the major concerns of cardiologists since it holds a very close relationship with the occurrence of ventricular arrhythmias. Hence, the assessment of VF/VT inducibility, effective refractory period (ERP), and other characteristics in patients with severe ventricular arrhythmias have been performed with invasive electrophysiological studies (EPS), including the assessment of drug effects. EPS is an invasive examination and repetition may be difficult. Simple and cheap methods for evaluating ERP and/or other electrophysiologic indices are still being sought.

The QT interval has been assumed to be a reflection of both ventricular depolarization and repolarization, and it is nearly equal to the summarized duration of action potential duration (APD) of global right and left ventricular cardiomyocytes. Thus, the QT interval has been assumed to be an apparent surrogate of ERP which can be measured on the ECG. Furthermore, the ECG is non-invasive, cheap, and repeatable as well.

Bazett focused on the QT interval in his famous paper published in 1920.[4] At that time he had already noticed that the QT intervals in various leads were not the same and also that the QT interval between males and females was not the same (i.e., gender differences as well as its heart rate-dependence).

Since the ECG is a reflection of cardiac electrical activity, it is important to understand ventricular depolarization and repolarization from the view point of electrical current flow. The heart contains many types of cells which are driven by electrical signals. The electrical activity of each cell reveals

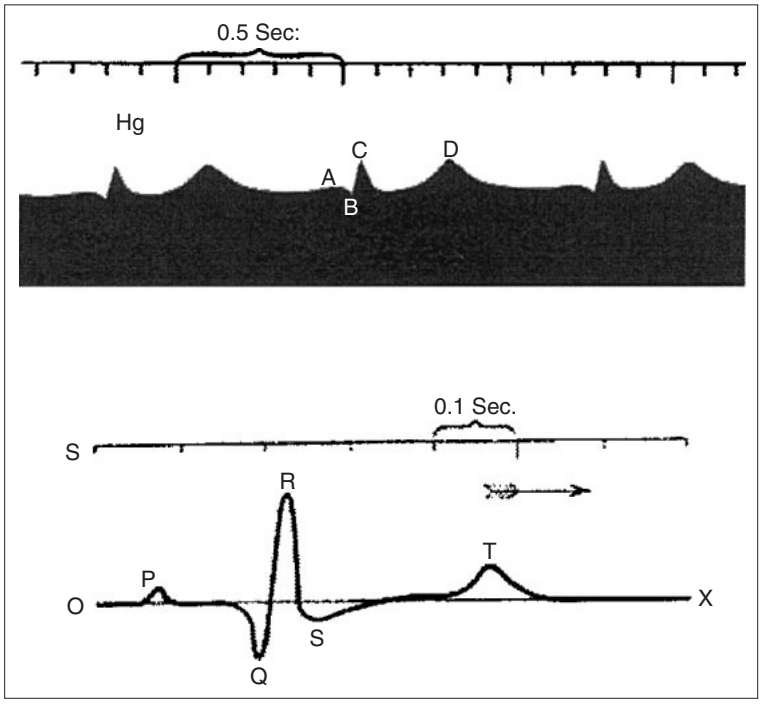

Figure 1 The electrogram recorded by Einthoven and its naming.
From ref. 2.

distinct action potential configurations which characterize cardiomyocytes from other excitable tissues, namely, a long action potential and a refractory period.

The list of variable cardiac electric currents, exchangers, and others are shown in **Figure 2**.[5,6] The cardiac ventricular action potential duration is influenced by variable conditions, such as electrolytes, autonomic nervous system transmitters, ischemia, peptides, hormones, and hypertrophy. The ionic currents and exchangers flow either inwardly or outwardly, depending on their electrochemical gradients.

Among all, the frequently involved ionic currents are iKr, iKs, ito, iNa, and iCaL, regarding the QT interval, since the action potential duration distinctly depends on a minute balance of those outward and inward currents, as illustrated in **Figure 2**. For instance, a small increase of iKr in the plateau phase does shorten the action potential duration (APD), whilst the block of the same current by a certain drug dramatically prolongs the APD according to the degree of blockade and hence the QT interval, known as acquired QT prolongation (reduction of repolarization reserve).[7–9] The inherited abnormality regarding such ionic currents certainly results in an abnormal QT interval and may be involved in the arrhythmogenesis, which is described later. Therefore, any genetic changes or synthesized compounds which modify inward or outward currents, ions or exchangers can modify the APD, resulting in QT interval changes. There is a long-lasting list of drugs, foods, and interventions with such actions.[10–12] From the clinical point of view, serum potassium level is important since it can modify the ventricular APD and the resting membrane potential. (**Figure 3**)

A prolonged QT interval and risk of sudden cardiac death is known to be closely related in populations of older adults.[13–15]

2-2. Prolongation of the QT interval

Prolongation of the QT interval can be attributed to the prolongation of ventricular APD, which is due to either the increased inward currents or the decreased outward currents.

The normal range of the QT interval is assumed to be no more than 450 ms in males and 460 ms in females.[16] Thus a QT interval longer than 460 ms is usually assumed to be prolonged. The congenital long QT syndrome is a well-known example. Patients with congenital long QT syndrome (LQTS) develop Torsades des Points (Tdp) that results in sudden cardiac death during childhood or youth. Up to now, 10 types of LQTS have been reported.[17,18] The details of LQTS can be found elsewhere.[19–21] Briefly, the decrease in iKs and iKr with an increase in iNa and iCa, has been identified to be due to inherited abnormal gene expressions (**Table 1**).

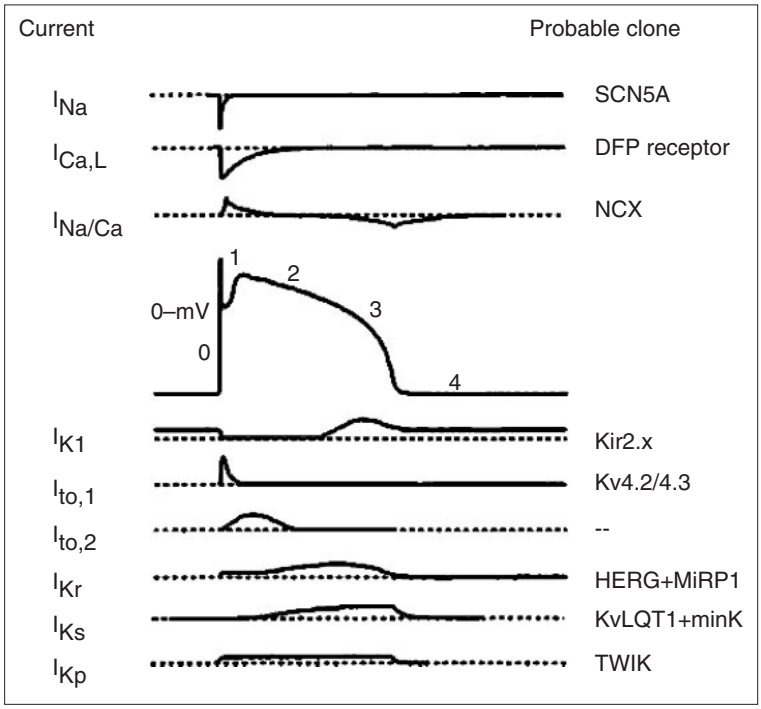

Figure 2 The four phases of action potential configuration and constituting inward (upper) and outward (lower) ionic currents and respective genes.
From Rosen MR & Cohen IS J Int Med 2006; 259: 7–23

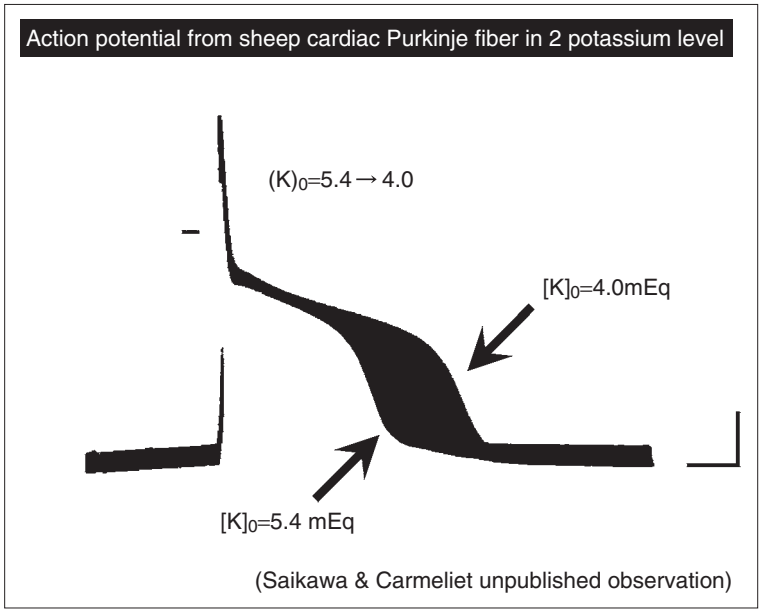

Figure 3 An effect of extracellular potassium level on sheep cardiac Purkinje fiver. Note the slight depolarization of resting membrane potential and the marked shortening of action potential duration.

Table 1 The list of gene abnormality.

•	LQT 1:	KCNQ1 (iKs)
•	LQT 2:	KCNH2 (iKr)
•	LQT 3:	SCN5A (iNa)
•	LQT 4:	ANK2 (Ankyrin 2)
•	LQT 5:	KCNE1 (iKs)
•	LQT 6:	KCNE2 (iKs)
•	LQT 7:	KCNJ2 (iK1)
•	LQT 8:	CACNA1C (iCaL)
•	LQT 9:	CAV3 (Caveolin 3)
•	LQT 10:	SCN4B (iNa)

Rearranged from reference 17 and 18

An acquired type of long QT syndrome is also well-known.[7,10] The most frequently encountered acquired QT prolongation is attributed to the block of iKr by variable agents, which eventually cause Tdp, resulting in sudden cardiac death. Many drugs have been withdrawn from the market due to such action and/or propensity to induce Tdp, not only in Japan, but also in other countries, although in some cases inherent abnormal gene expression coexists.[22–24] However, in most cases, the victims of Tdp exhibited a prolonged QT interval, usually accompanied by the combination of iKr blocking agents with a low potassium level and bradycardia.[7,25]

It has been *a priori* assumed that the prolongation of the QT interval is arrhythmogenic; there is little information, however, regarding how much of the prolongation is arrhythmogenic. So far few reports have mentioned the distinct level of prolongation or definite values of QT interval to be arrhythmogenic. Joshi et al. analyzed 35 cases of Tdp.[26] They reported that at least a 25–30% prolongation of the QT interval from baseline was noted in cases of Tdp, and a mean nominal value of QT interval increase in cases of Tdp was approximately 201 ms (48% increase; the absolute mean QT interval was > 600 ms in Tdp patients), whilst no Tdp developed in patients who showed a QT interval < 500 ms. They also described that the QT prolongation and amplification of transmural dispersion of repolarization (TDR) was a powerful determinant of developing Tdp.[26]

Previous reports[27–30] have also suggested that the association between a prolonged QT interval and proarrhythmic risk may not be straightforward by both clinical and experimental observations: 1) different drugs causing comparable absolute or relative increases in repolarization do not always result in similar Tdp incidences and 2) in serial experiments using various doses of the same drug, proarrhythmic outcome is not dependent on the degree of the QT interval prolongation,

Calmodulin kinase II inhibitor can abolish both EAD and DAD without changing the APD,[31] strongly suggesting that the interrelationship between the APD and arrhythmogenicity is not always direct and not an unbreakable connection. These arguments are all consistent with the notion that the simple prolongation of the QT interval is not necessarily arrhythmogenic, but the accompanied

increased heterogeneity of repolarization and/or the exaggerated beat-to-beat variability of repolarization is arrhythmogenic.[32] Thus, it is not just a matter of the QT interval prolongation, but a matter of the heterogeneity of repolarization.

2-3. The shortening of the QT interval: The short QT syndrome

The shortening of the QT interval is attributed to the shortening of the APD due to an imbalance of inward and outward electric current flow.

The nominal range of a normal QT interval is often described as < 450 ms in males and 460 ms in females. However, this denotes only the upper limit of the QT interval, without commenting on the lower limit of the index.[16] Thus, only the upper limit of the index has been focused upon and discussed until quite recently. Certainly, the lower limit of the QT interval does exist and it may be around 350 ms according to Rautaharju et al.[16] There has been no active discussion on the lower limit of the QT interval until now. Shortening of the QT interval, however, has not usually been assumed to entail an increased risk of arrhythmia.

The congenital long QT syndrome is a one extreme side of a QT interval abnormality. The recent report of sudden cardiac death associated with a short QT interval[33–35] opened the door to the other side of extreme QT interval abnormality.

Gussak et al. reported an extremely short QT interval in a 17-year-old Caucasian female patient with a QT interval of 280 ms at a heart rate of 69 bpm.[33] They also reported a case of a 37-year-old female with a very short QT interval who suddenly died while waiting for an EPS. According to a formula[16] for prediction of the QT interval from a patient's heart rate, QTp (msec) = 656/(1 + heart rate/100), all the patients in the Gussak et al. study had a QT interval below 80% of the predicted value. Further, the ECGs of the short QT interval patients with associated ventricular arrhythmias showed tall, peaked T waves and broad Tp-e intervals, suggesting increased TDR.[36] The syndrome also showed a high incidence of supraventricular tachyarrhythmias, such as atrial fibrillation. Clearly there is a normal range for the QT interval, with a lower and upper limit.

Like LQTS, SQT is now classified into 3 types depending on their gene mutations: 1) SQT1[37] (ERP < 150 ms and VF inducible; KCNH2 (iKr) mutation); SQT2[38] (ERP < 180 ms and VF not inducible; mutation in KCNQ1 [KvLQT1; iKs]); and SQT3[39] (ERP 160 ms and VF inducible; mutation in KCNJ2 [iK1]). Thus it seems that it is better if the value of the QT interval is between the lower and upper extremities, which can be considered "a happy medium".

Up to now, no short QT syndrome patients have been reported in Japan.

3. The Dynamics of the QT Interval

3-1. Heart rate correction of the QT interval

The QT interval is dependent on the heart rate. The dependence has been analyzed since the days of Bazett, and many formulae have been developed to correct the QT interval to the heart rate. The oldest one, Bazett's formula, overcorrects when the heart rate increases, as Simonson pointed out in 1962.[40] Since then, several formulae, such as the Fridericia,[41] Framingham,[42] and Hodges[43] formulae, have been developed and introduced. However, the oldest one, the Bazett's formula, is still in current use according to some of the literature, including those in the field of cardiology. According to recent publications, the Van de Water,[44] Framingham, and Hodges formulae are well-assessed and reveal a rather good relation. Luo et al.[45] analyzed human ECGs from a database using four correcting formulae. Consequently, the distribution of the QTc showed the QTc corrected with Bazett's formula were distributed differently than the others, corrected by Fridericia, Framingham, and Hodges formulae.

Milic et al.[46] analyzed the effects of beta2 agonist-induced QT prolongation and concluded that using the Bazett formula may be misleading with regard to the real effects of QT prolongation by various drugs. The magnitude of formula-dependent differences of the QT interval may reach to 20–30 ms, which is rather significantly large for the requirements of ICH E14 and S7B.[47]

Recently, the QT-RR relationship in a healthy population has shown a substantial inter-subject variability and high intra-subject stability. Batchvarov et al.[48] analyzed 12-lead 24-hour ECG recordings which was repeated after 24 hours, 1 week, and 1 month in 75 healthy subjects. They compared intra-subject stability with inter-subject variability and concluded that the QT-RR interval relationship showed substantial inter-subject variability, as well as a high intra-subject stability. For example, the slope of the linear QT-RR model ($QT = \alpha x RR + \beta$) in their study ranged from 0.137 to 0.199 in males and 0.145 to 0.243 in females. On average, males had an α of 0.163 and a β of 0.242, while in females the α was 0.203 and the β was 0.225. The results indicated that at a rate of 60/min, the QT interval could vary between 62 ms, which would be far beyond measurement error.

Malik et al.[49] also reported similar results. They showed that in a linear model ($QTc = QT + \alpha$ (1-RR)), α ranged between 0.0928 to 0.2577, with a mean of 0.1713. While in a parabolic model, like $QT = QT/RR^{\alpha}$, α ranged between 0.233 and 0.485, revealing the QT ranged between 379 and 401 ms at a rate of 75/min. At 85/min and 95/min, this difference increased to 390–426 msec and 401–450 msec, respectively. Thus, the choice of which QT correction formula to use does influence the results of the correction substantially.

Further, Smetana et al.[50] analyzed the circadian rhythm of the QT interval using different heart rate correction formulae of the QT interval. They used five different correction formulae, i.e., the Bazett, Fridericia, Framingham, and Hodges, and an individual formula derived from the individual QT-RR relation. Interestingly, they found that the QTc circadian rhythm disappeared by using the Bazett formula, as shown in **Figure 4A**. We also analyzed the circadian variation of the QT interval and noted that although the QT interval revealed significant circadian rhythm, the QTc corrected by Bazett's formula did not show circadian variation.[51] Thus, the results were consistent with our results and from the results of Smetana.[50] They also concluded that the inconsistency of the presence or absence of this circadian variation of the QT interval might depend on the methods used for heart rate correction.

The testimony of the above heart rate correction formulae indicated that the individual formula disclosed the most heart rate independence, as shown in **Figure 4B**. This means that averaging the QT correction with a certain formula is potentially hazardous and might produce a false QT prolongation or shortening. For developing new drugs, a much more cautious measurement of the QT interval is necessary. The QT-RR relation seems to have been modulated in patients with congenital long QT syndrome.[52] The QT-RR relationship was also modified in patients with a long QT syndrome with an apparent normal QT interval, such as before and after beta blockade treatment.[53]

We analyzed the QT-RR relationship in 32 patients with sick sinus syndrome, i.e., those with episodes of prolonged RR intervals (longer than 2.6 seconds).[54] We classified the patients into two groups: 1) no QT prolongation (< 0.44 sec) at a heart rate of 60/min and 2) prolonged QT interval (> 0.44 sec) at 60/min. They found that the slope of the QT-RR relation was significantly larger in those with a prolonged QT at 60/min. The results meant that patients with a prolonged QT revealed a larger QT interval increase as the RR interval increased.

However, one should keep in mind that all these data were collected by computer assistance, and little verification was performed by a QT specialist. There is a choke point here for measuring correct and precise QT interval. The golden standard here for the measurements of the QT interval is the human eye. Therefore the same critical issue remained as the determination of the T wave end.

Taking all of these into consideration, the QT-RR relationship was also modified by the underlying pathophysiology, and we should be cautious when assessing the QT interval from a variety of patients.

3-2. Dispersion of the QT interval: Four-dimensional dispersion

3-2-1. Spatial dispersion

We may say that there are two types of dispersion, spatial and temporal dispersion. The onset of the QT interval and the offset of the QT interval are rather difficult to recognize; however, apparently it seems to disperse. The issue is whether the dispersion of the QT onset and offset really reflect a local dispersion of heterogeneity of repolarization. The notion of so-called QT dispersion proposed by the group of Campbell,[55,56] who passed away in 1998,[57] has invaded the electrocardiology field and numerous papers have been published, including ours.[51,58,59] This QT dispersion, however, has been controversial in recent times. Assuming that the ECG is a reflection of the cardiac vector loop to the respective plane, the angle between the axis and vector loop projection is critically important and may compromise the T wave end identification in certain conditions. Namely, the projected loop may lap over on the isoelectric baseline, which underestimates the end of the T wave and then the QT interval. The end of the T wave apparently seems to be dispersed. However, this may simply be an artifact due to the heterogeneous overlap of the ECG tracing on the isoelectric baseline and may not be a surrogate marker of ventricular repolarization heterogeneity.[60,61] Therefore, one has to measure the QT interval from the earliest onset of the QRS complex to the latest end of the T wave, which is the longest QT interval.

Recent studies have emphasized the role of TDR; the increase in the TDR is proarrhythmic and its decrease is antiarrhythmic.[36,62,63] TDR is proposed by the group of Antzelevitch[64] and is calculated as the time interval between the peak of the T wave to the end of the T wave, deduced from their wedge preparation experiments. Many studies have been done using this index as a surrogate of transmural heterogeneity of repolarization. Further, a recent

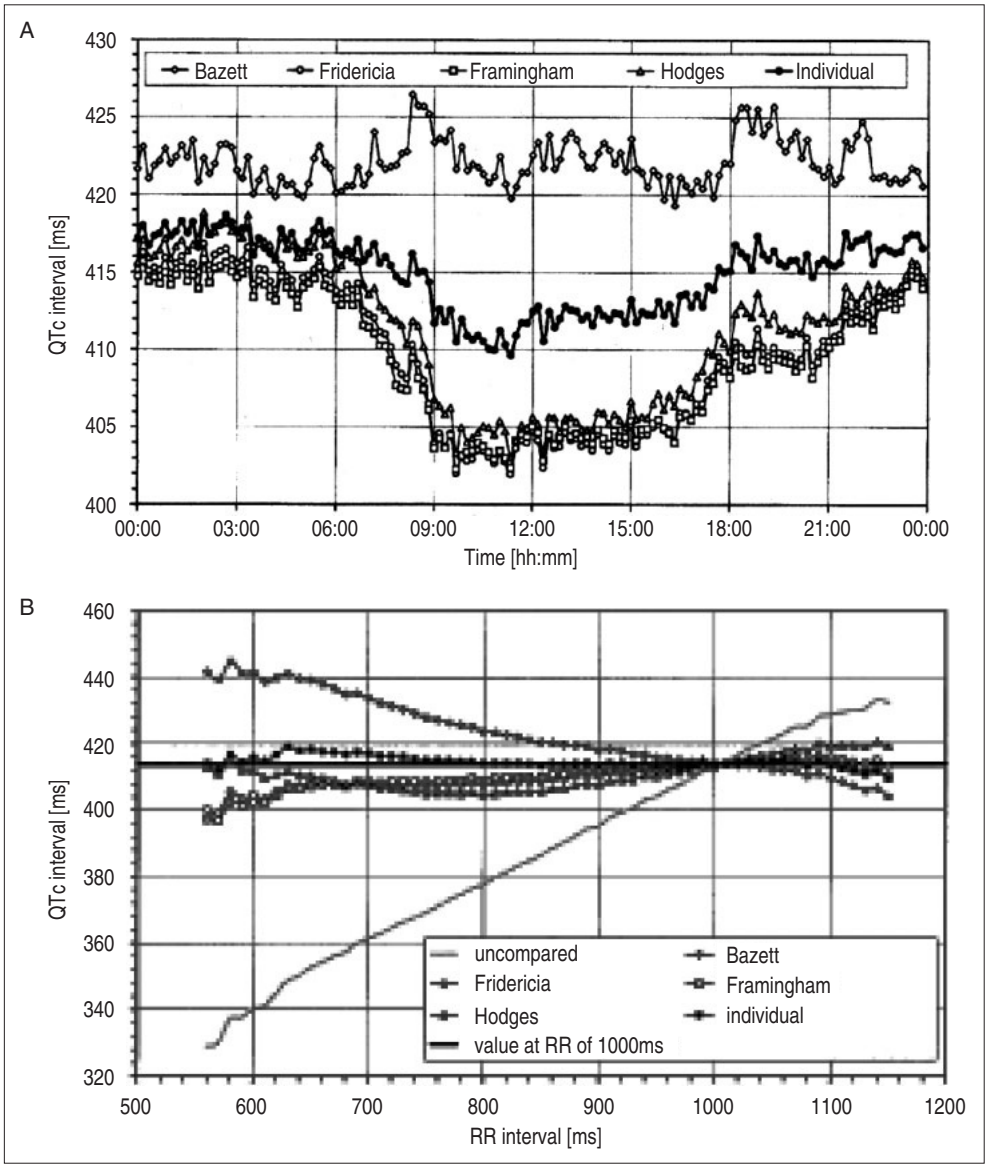

Figure 4 Circadian variation of QT interval corrected by variable formulae and their heart rate dependence.
From Figure 2 & 3 from ref. 50.
Note that the circadian variation disappears by correction using Bazett formula.

review[36] described an increased TDR in patients with cathecholaminergic ventricular tachycardia, long QT, short QT, and Brugada syndrome. Therefore, the TDR seems to be a promising index, a seeming white knight, instead of QT dispersion. Once again, we have to face, however, the issue of measuring the end of the T wave. It might be better to reserve TDR for the next step as an index of heterogeneous repolarization through the ventricular wall. The heterogeneity of repolarization does exist, even physiologically due to heterogenous action potential duration;[65–67] however, the problem is its detection method.

The QT dispersion still needs theoretical support to justify that it reflects a local heterogeneity of repolarization. TDR may also require theoretical support.

3-2-2. Temporal dispersion

There is another type of dispersion or heterogeneity of repolarization and/or QT interval. The QT interval is not fixed, and may change as time goes by owing to variable reasons, such as ischemia, fibrosis, and remodeling induced by variable cardiovascular overload, as well as short-term endocrino-

logic variation. Namely, the QT interval shows both short-term and long-term variation. This line of variation or heterogeneity is designated as temporal dispersion.

One extreme pattern of temporal dispersion may be a beat-to-beat variability of the QT interval. Focusing on this beat-to-beat variability of the QT interval, a novel index was invented.

Berger et al.[68,69] hypothesized that abnormal beat-to-beat changes exist in ventricular repolarization and developed a novel algorithm for QT interval assessment. They computed the heart rate mean (HRm) and variance (HRv) and the QT interval mean (QTm) and QT variance (QTv). A normalized QT variability index was then calculated as follows: QTVI (QT interval variability index) $= \log_{10} \{(QTv/QTm^2)/(HRv/HRm^2)\}$ The QTVI represents the log ratio between the QT interval and heart rate variability, each normalized by the squared mean of the respective time series. In patients with DCM, the heart rate varied little and the QT interval fluctuated widely and unpredictably, while in control subjects, the heart rate variability was large and the QT variability was small. QT interval variability increases with worsening functional NYHA class. QT interval variability is a parameter of temporal dispersion of repolarization and seems to be a marker of increased risk of developing life-threatening arrhythmias and sudden cardiac death. QT interval variability is also associated with increased risk for VT/VF in MADIT II patients.[70,71]

Piccirillo et al.[72] analyzed the long-term beta blocker therapy on patients with chronic heart failure secondary to ischemic cardiomyopathy in 130 patients. They randomized the patients into carvedilol and metoprolol groups and investigated the effects of the drugs in head up tilt before and after treatment. Both agents lowered the QT interval variability and carvedilol seemed to improve the QT interval variability index more than metoprolol. Thus, the authors concluded that the QTVI may be useful for stratifying patients at high risk for ventricular tachycardia and ventricular fibrillation.

Piccirrillo[73] also reported that the QTVI is helpful in stratifying the risk of sudden death in this otherwise undertreated population in 396 patients with chronic heart failure due to post-ischemic cardiomyopathy, with an LVEF between 35 and 40% and in NYHA class I.

Thomsen et al.[74,75] recently reported a new index of beat-to-beat variability of repolarization (BVR) using Poincaré Plots in animal experiments. They analyzed proarrhythmogenecity using left ventricular monophasic action potential duration (LVMAPD) and the QT interval with the analysis. They concluded that beat-to-beat variability of LVMAPD (beat-to-beat variability of ventricular repolarization [BVR]) could predict the proarrhythmic action of both cardiac and non-cardiac agents, but not that of the QT interval. Thomsen et al. also described that the canine group, which developed the increased BVR, has a tendency to be proarrhythmic.[76] Unfortunately, the usage of LVMAPD instead of the QT interval is not applicable in a daily clinical setting. Hence, if the QT interval is not available for analysis, more sophisticated non-invasive parameters may be necessary instead of the LVMAPD. Anyway, the assessment of this beat-to-beat variability may be promising to understand why certain arrhythmias arise on some special occasions and why it did not develop on other similar occasions.

4. The Morphology of the T Wave

The morphology of the T wave is also interesting. The postextrasystolic potentiation of the U wave is observed in patients with organic heart disease and in those with congenital long QT syndrome. This phenomenon is assumed to be associated with an increased risk of an arrhythmic event.[77] The U wave designated here is not the same as the U wave which is noted in healthy people. The U wave we define here is the wave which encroaches to the descending limb of the T wave and some may call a notch or a hump on the T wave or T-U complex, while the U wave, in the usual sense, is the wave which begins after the T wave terminates and follows the return of the T wave to the isoelectric baseline.

We previously reported seven cases of acquired Tdp.[78] In all 43 episodes from the 7 cases, the long-short initiating cycle and R on T (U) phenomenon were confirmed in 42 among 43 Tdp episodes. The QT interval just prior to the onset of Tdp was increased as compared with the QT recorded 6–24 hours before. In most cases, the morphology of the T wave changed and the notch (U) on the descending limb of the T wave was seen (**Figure 5A**); furthermore, the amplitude of the U wave and U/T ratio increased when U wave was followed by a PVB and Tdp, resulting in an increased ratio of U/T, irrespective of the underlying heart rate (**Figure 5B**).

We also analyzed the kinetics of the notch/U wave in the idiopathic ventricular tachycardia (VT) originating from the right ventricular outflow tract (RVOT).[79] The so-called RVOT-VT seems to share a common characteristic, as above (**Figure 5C**).[79] In these patients, after the return of the T wave to baseline, the U wave was seen. Interestingly, as the

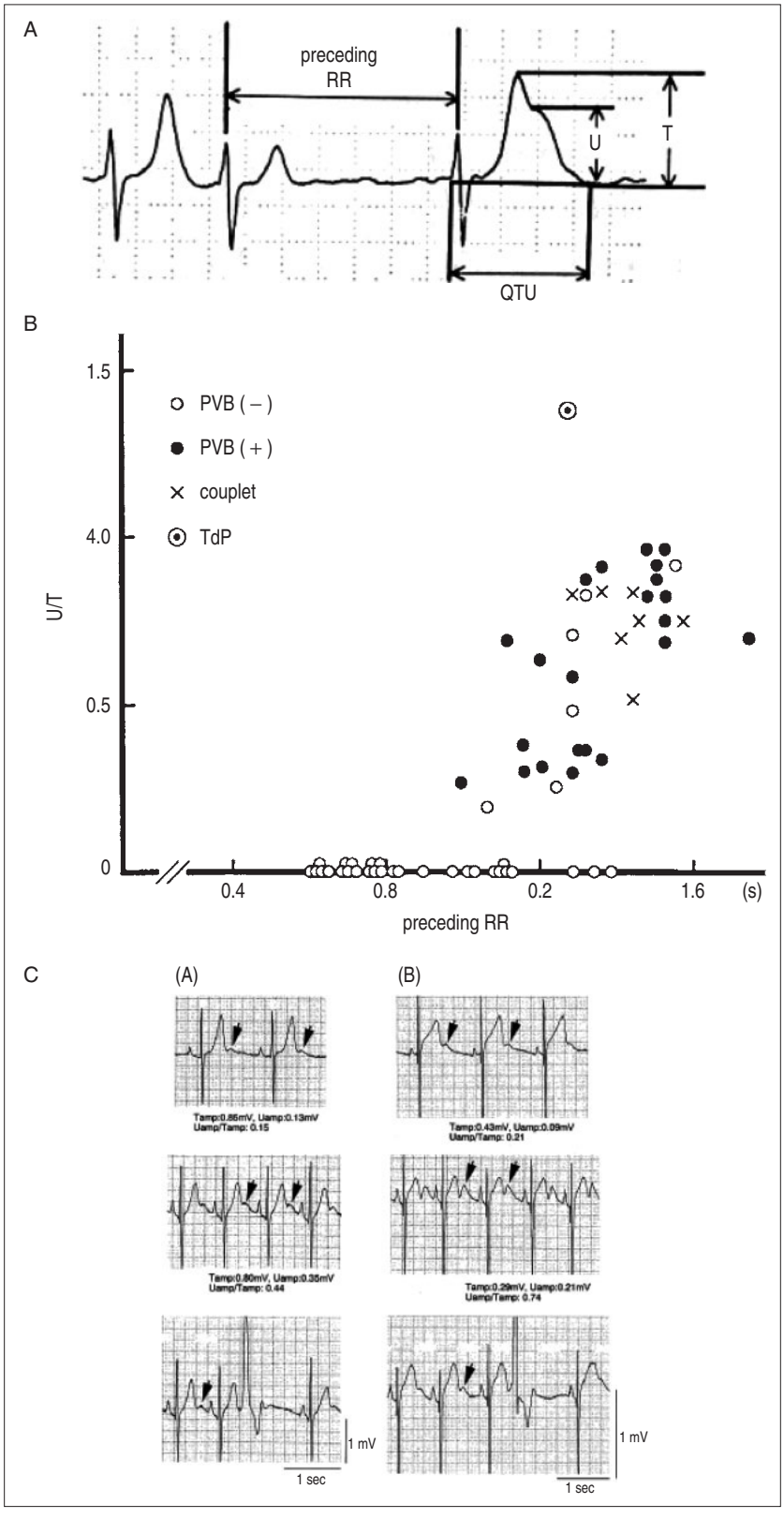

Figure 5
A: The measurements of the amplitude of T and U waves. B: The plots of preceding RR and U/T ratio. C: A PVC took off from the notch or hump of T wave descending limb. From ref. 78 and 79.

rate and the number of premature ventricular beats (PVC) in the runs increased, the amplitude and coupling interval of the U wave grew and encroached upon the descending limb of the preceding T wave, and finally the two waves fused and formed a notch, the so-called T-U complex or T1 and T2 wave.[80] Frequently, the T2 wave becomes larger than the T1 wave following runs of PVCs and occasionally the PVC took off from the T2 wave,[80,81] as shown in **Figure 5C**. The amplitude of the T2 wave becames larger, even though the diastolic interval increased. The mechanisms of the augmentation of the T2 wave are interesting. Apparently three different mechanisms may be possible: 1) early after-depolarization (EAD), 2) delayed after-depolarization (DAD), and 3) mechano-electrical feedback.[82] Viskin et al.[82] attributed this "U" wave noted in such a condition to the last candidate shown above, mechano-electrical feedback.

There is an interesting report[83] describing an acceleration-induced action potential prolongation and EAD. They showed that the sudden acceleration of the pacing cycle length from a range of 900 to 2,000 ms to a range of 500 to 1,500 ms induced transient EAD activity and increased the EAD amplitude in canine M cells. The acceleration usually abrogates EAD and accompanies an abbreviation of APD. Within discrete ranges of physiologic rates, however, acceleration caused a transient prolongation of APD in 38% of the M cells. These characteristics may also explain the behavior of the U wave noted in the RVOT-VT reported in our paper.[78] Thus, as described in our paper, the possibility remains that EAD is the cause of the "U" wave.

The T wave morphology is extremely important, especially if adverse events occur under the administration of antiarrhythmic agents. Viskin et al. also described an interesting T wave morphology change in patients with acquired long QT syndrome.[84] They showed that variable changes in T wave morphology depended on serum levels of potassium, administered drugs, and other environmental influences. Merri et al.[85] tried to quantify the ECG changes according to the 11 ECG indices. They analyzed seven indices of ventricular repolarization characteristics. Among them, Tm-To was designated as "late duration" and was independent from both the heart rate and the QT interval and was one of the independent indices of ventricular repolarization. It is a strange but interesting coincidence that Tm (T wave absolute maximum) - To (T wave offset) is a similar variable as subsequently proposed by Antzelevitch et al.

5. Conclusion

Regarding the analysis of the QT interval, it is not just a matter of the interval itself, but is also relates to heterogeneity and abnormal T waveforms. We cannot emphasize too strongly the importance of analysis of this T wave morphology. We also need a breakthrough for measurements of the QT interval since the overlapping of the T wave end with the isoelectric line is inevitable using the present methods. The secular change in the position of heart and body shape will also modify the vector loop, and consequently the T wave end overlaps on the isoelectric line and obscures the true end of the T wave. At the same time, heart rate correction is also important and the correction may mislead the results in certain cases.

Regarding the QT interval, Japanese have the saying, "For everything, to steer between two extremities is important," (*Nanigotomo hodo-hodo ga yoi*. in Japanese). Taking the top or bottom value will not always give us the right answer. However, this statement is limited to the QT interval, and cannot always be expanded to other areas.

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