QT Dynamicity: Clinical and Prognostic Implications

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Evaluation of ventricular repolarization parameters has been for years considered as one of the major concern in contemporary electrocardiology. Such assessment includes both simple description of QT interval duration as well as evaluation of its dynamic behaviour (1-12). QT interval reflects entire ventricular repolarization. Prolonged or too short QT, as well as increased QT dispersion reflecting increased heterogeneity of myocardium intervals have been described as risk factors for development of malignant arrhythmia and an increased risk of sudden death (13-15). Nevertheless, the prognostic value of static repolarization parameters remains controversial. It is known, that QT interval may be influenced by various factors as heart rate, sympathovagal balance, metabolic status or drugs (16-20). Tendency to tachycardia preceding malignant arrhythmias as well as an abrupt prolongation of QT interval were reported in sudden death victims (21-23). Evaluation of repolarization process limited to merely QT interval duration in a standard surface ECG may not correspond to what happens in the period directly proceeding malignant arrhythmias. Therefore, evaluation of QT adaptation to changes in heart rate has gained more importance in sudden death risk stratification. Furthermore, as repolarization process may be influenced by variety of drugs leading to unfavourable proarrhythmic effects more and more attention is paid to QT dynamicity in the process of drugs safety evaluation (24,25). Advances in Holter technology in recent years allowed for continuous tracking of RR intervals and corresponding QT intervals and brought an increased interest in the analysis of dynamic behaviour of repolarization.

Methods to assess repolarization dynamics

There exist different methods to assess repolarization dynamicity. The most widely used method estimates QT/RR slope. QT dynamicity is then measured by the slope of the linear regression between QT and RR intervals. Measurement is performed separately for both QT apex (*QTa)* and QT end (*QTe*). In contrast to QT adaptation this method refers rather to flexibility of QT and in terms of time is a matter of seconds. This parameter currently may be measured in standard commercial Holter equipment therefore QT and RR values may be linearly correlated over 24 hours. Increased QT/RR values indicate excessive lengthening of QT at slow rates or excessive shortening at fast rates. Both of these mechanisms may significantly contribute to sudden death. Steeper QT/RR indicates decreased vagal tone and increased sympathetic activity reflecting the higher vulnerability of myocardium to arrhythmias. At the cellular level sympathetic stimulation

prolongs ventricular refractoriness. Therefore, increased QT slope represents increased vulnerability of myocardial substrate to its modulation by autonomic nervous system (12,19,20,26).

There is no consensus on so called “normal values” of QT/RR dynamicity and a significant inter- and intravariability have been reported (27,28). Consequently, abnormal QT/RR parameters are routinely expressed as those from upper quartile having on mind that steeper QT/RR slope reflects excessive shortening of QT with fast rate and/or excessive lengthening of QT with slow rates.

Our group developed a method of describing abnormal behaviour of QT interval expressed as the percentage of abrupt QT interval prolongation over predetermined threshold detected on 24 h Holter monitoring named as QT peaks (10,11). Peaks of QTc lengthening were defined as the presence of intermittent QTc values longer than a determined cut-off point (500 ms). Furthermore we considered that clusters existed when the peaks were grouped and lasted at least 1 minute. Transitory QT lengthening may express a temporal imbalance of the autonomic nervous system that may lead to heterogeneity of the ventricular refractory periods and may predispose to the development of reentry phenomena. Our algorithm also allowed to detect peaks of excessive QT dispersion defined as the presence of QTd>100 ms.

Jensen et al (26) decribed a novel QT dynamics parameter called as QT/RR variability ratio (VR) defined as the ratio between the standard deviation of all QT intervals and the standard deviation of all RR intervals.

Clinical covariates of QT dynamicity

In normal conditions, QT interval is modulated by variety of factors, like heart rate, circadian rhythm, autonomic nervous system or hormones.

QT dynamicity is known to be influenced by variety of clinical covariates. Relationship between QT/RR dynamicity and age was reported in healthy subjects (29). Similarly, gender related differences in repolarization were reported, showing that women tend to present higher QT/RR slopes (29-31). This might support the theory that QT dynamicity is influenced not only by autonomic nervous tone but also by other factors like hormones.

QT/RR slope was found to be a strong marker of existing cardiac pathology. Abnormal QT dynamicity was found in different populations including patients with long QT syndrome, ischaemic heart disease, dilated and hypertrophic cardiomyopathy, congestive heart failure, obstructive sleep

apnea or diabetes (32-38). On the other hand lower values of QTa/RR slopes were observed in patients with idiopathic ventricular fibrillation (39).

Impaired dynamicity of repolarization may be related to the degree of left ventricular dysfunction as well as may progress with severity of symptoms in patients with heart failure (34,40). This is also supported by our experience based on a large population of patients with heart failure included into MUSIC study (Muerte Subita e Insuficiencia Cardiaca = Sudden Death in Heart Failure) (41).

The night/day variation in QT/RR slope was reported and explained both by differences in heart rate as well as by different sympatho-vagal status (26,29,30). Such circadian changes are abolished in patients with heart failure showing the loss of circadian modulation attributed probably to impairment of autonomic nervous system in these patients (16,34).

QT dynamicity joints together all pathophysiological factors known to modulate QT interval such as heart rate, sympathovagal tone, metabolic status and drugs and therefore puts together repolarization and autonomic nervous system assessment. Abnormal repolarization dynamicity is considered as a marker of myocardial vulnerability contributing to increased risk of arrhythmic events and sudden death.

In respect to QT peaks, we documented that patients with dilated cardiomyopathy in comparison with healthy subjects present higher number of QTc peaks (over 500ms) as well as QTd peaks (over 100ms). These parameters were significantly higher in DCM patients after adjustment for age, sex, and heart rate variability (42) . In postinfarction patients we observed a specific circadian rhythm of QT dynamicity with a significantly higher incidence of QTc peaks between 11 pm and 11 am (10)

Prognostic value of QT dynamicity

Dynamicity of QT may be considered as a marker or as a trigger for malignant arrhythmias and/or sudden death. A few case reports showed abrupt changes in QT/RR values before onset of malignant ventricular arrhythmias (22,23). This may indicate that an abrupt increase in QT/RR slope steepness may be a trigger for terminal rhythm disturbance. On the other hand abnormal behaviour of repolarization dynamicity may be considered as a marker of increased risk of death. Abnormal values of QT/RR slope were found to predict cardiac events in various populations, mainly in postinfarction patients (33,37,43,44,45). Furthermore, such a pattern of dynamic repolarization was a stronger predictor of sudden death than all-cause mortality suggesting

stronger relationship of this risk marker to increased vulnerability of myocardium to ventricular arrhythmias. Milliez et al. (45) in a substudy from EMIAT Trial found that steeper QT/RR predicted arrhythmic events in postinfarction patients. Similarly, Chevalier et al. (44) showed that in early postinfarction period increased QT/RR slope is an independent risk predictor of sudden death. The hazard ratio for daytime QTe/RR slope (over 0.18) was 3 times higher than to prediction of total mortality. Similar pattern was observed in a study of Pathak et al. (37) who found that increased QTe/RR slope assessed over 24 hours was predictive for sudden death in patients with chronic heart failure due to ischemic (43%) or idiopathic (57%) cardiomyopathy with mean LVEF 28%.

We observed that increased number of peaks of prolonged QTc interval is a marker of life-threatening arrhythmias in postinfarction patients (10). The prognostic value of QT peaks in patients with heart failure remains to be established.

QT/RR variability ratio independently predicted all-cause mortality in postinfarction patients in a study of Jensen et al. (26)

QT dynamics and drug safety

Apart from being used in sudden death risk stratification, evaluation of repolarization parameters has become one of the main policies in the process of drugs safety assessment (24,25). Nevertheless, little data exists on the influence of drugs on QT dynamicity and the published results are contradictory. Studies evaluating QT/RR as a risk predictor frequently exclude patients on amiodarone and beta blockers for risk stratification. The effects of beta blockers on ventricular repolarization are conflicting. Beta blockers were found to reduce or to show no effect on QT/RR slope (46,47). Verapamil was documented to significantly shorten QT intervals at lower heart rates (48). Drugs class III like amiodarone and dofetilide were reported to influence QT/RR slopes (49,50).

Further directions in QT dynamicity assessment

Evaluation of QT/RR slope has become one of the most popular method, however various forms of dynamic behaviour of QT interval exist.

There is an increasing interest in the analysis of dynamic changes in repolarization parameters. Apart from QT dynamicity relating QT interval duration with heart rate changes more and more attention is paid to morphological changes in T wave described as QT variability or T wave alternans (51,52). Berger et al. (51) developed an algorithm to quantify changes in repolarization

duration and morphology. Increased beat-to-beat changes in repolarization duration and morphology predisposes to electrical instability of myocardium and may favor initiation and maintenance of reentry arrhythmias. Microvolt T wave alternans, reflecting beat-to-beat 2:1 changes in the amplitude and sometimes the polarity of repolarization is another well-known marker of arrhythmic events.

Summing up, dynamic assessment of QT interval enables to evaluate the complex interaction between variety of factors known to influence ventricular repolarization. Abnormal dynamicity of repolarization constitutes an important marker of underlying pathology of the heart and/or autonomic nervous system and is documented as a strong risk predictor of increased mortality. Of note, impaired dynamicity of repolarization is of special interest in prediction of arrhythmic events and sudden death.

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