COMMENTARY

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Drug-Induced Changes in the T-Wave Morphology

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The understanding that different non-antiarrhythmic drugs may alter ventricular repolarization and thus lead to potentially harmful proarrhythmia is only some 2 decades old.[1-4] The need to test practically all new drugs for such effects, mainly the induction of torsade de pointes (TdP) tachycardia, emerged from this knowledge and led to the present conception of the so-called thorough QT studies.[5] As is well known, the concept of thorough QT studies is based on the investigation of the drug-induced changes of the heart rate corrected QT (QTc) interval duration. It is also well understood that the relationship between proarrhythmic liability of the TdP type and drug-induced QT interval prolongation is not without problems.[6] While there are compounds that do prolong QT interval but do not cause TdP tachycardia, tests of proarrhythmic liability based on QTc interval assessment seem to have practically absolute sensitivity. Every drug that has so far been observed to cause arrhythmia of the TdP type has also been found to change QTc interval substantially if given in sufficiently high doses. This is also the reason why the present regulatory practice requires drugs that prolong QTc interval to be investigated more intensely in the later phases of clinical development so that their proarrhythmic TdP-type toxicity can be eliminated, or at least properly characterized, for the purpose of benefit-risk evaluation.

Hence, it is the lack of a very high specificity that makes the drug testing based on QTc interval changes unpopular, not only among drug developers but also among academic investigators. Early on in the era of understanding the proarrhythmic toxicity of non-antiarrhythmic drugs, academic consensus emerged – spelt out during various review lectures and keynote presentations – that the assessment of drug safety based on QT interval measurements would soon be replaced by studies of drug-induced changes in the morphology of electrocardiographic repolarization signals, i.e. changes in T-wave shapes and patterns. Although this consensus was based more on wishful thoughts rather than on any solid data, it gained widespread popularity. Indeed, some years ago, the very author of this commentary repeatedly predicted that by now, QT interval measurement would have been abandoned in drug development.[7] However, in spite of the widespread academic enthusiasm and focused work by various centres, this methodical development failed to materialize. With the benefit of hindsight, one can list a full scale of different reasons why proarrhythmic assessment in drug development still relies on QT interval measurements and why this is likely to continue in the foreseeable future.

The first problem is perhaps with the individuality of repolarization electrophysiology. Several characteristics of repolarization dynamics have been found to be highly variable between different individuals, while being remarkably stable and reproducible within each subject.[8,9] They include both the QT/RR profile, that is, the extent to which the QT interval changes if the underlying heart rate changes, and the QT/RR

hysteresis, that is, the speed with which the QT interval responds to the changes in heart rate. The term 'repolarization fingerprint' has sometimes been used to point out the resemblance between the intra-subject differences in repolarization properties and the individual-specific dermal papillae. At present, methodology exists for coping with the individuality of QT interval adaptation to heart rate changes, but even an elementary basis of such methodology is missing for the assessment of T-wave morphologies. It is known that T-wave morphologies (and thus their many descriptors) are individually dependent on heart rate[10] (figure 1) and other co-variates, but controlling for these has never been attempted. The necessary basic methodological research is still lacking.

The problem of inter-individual variability is linked to measurement stability. The advanced methods for correcting the QT interval for heart rate and QT/RR hysteresis allow the QT interval-based measurements to be made highly reproducible within each subject, thus allowing highly controlled experiments.[11] On the contrary, various characteristics of T-wave morphology are much less reproducible even without any drug provocation (figure 2). This pattern variability is possibly due to higher sensitivity of T-wave morphologies to multitudes of co-variates that are difficult not only to control but also to account for. Our knowledge on the intra-myocardial processes that change the T-wave morphology and that might therefore complicate any drug experimentation is presently fairly limited. The so-called T-wave memory[12] and post-ectopic T-wave changes[13] are good examples of phenomena that involve mechanisms that we do not know how to eliminate, and thus how to deal with, in clinical studies.

This all turns into yet another problem. It seems fairly reasonable to expect that drug effects on repolarization morphology are due to a combination of drug influences of different ionic channels in different layers and regions of the ventricular myocardium. (None of the drugs can be characterized as having absolutely exclusive effects on only one channel type.) Not only is the combination of these drug effects likely to be

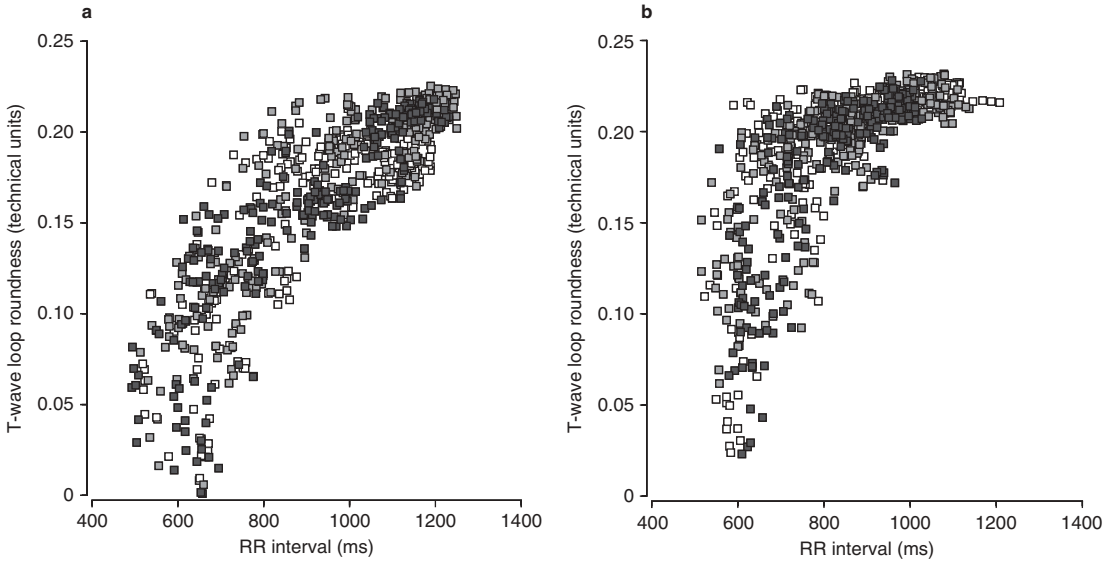

Fig. 1. Dependency of the 'roundness' of the three-dimensional T-wave loop on heart rate (expressed as RR intervals, i.e. the time elapsing between two consecutive R waves on the ECG) in two different healthy subjects (**a** and **b**) not taking any medication. The 'roundness' of the T-wave loop is measured in technical units; the lower the value, the more sharp peaks are seen in the T-waves. The open, light-shaded and dark-shaded squares correspond to three different recording days, each separated by a period of at least 2 weeks. Note that while the 'peakedness' of the T-waves is rate-dependent in both cases, the profile of the dependency is reproducibly different in both individuals.

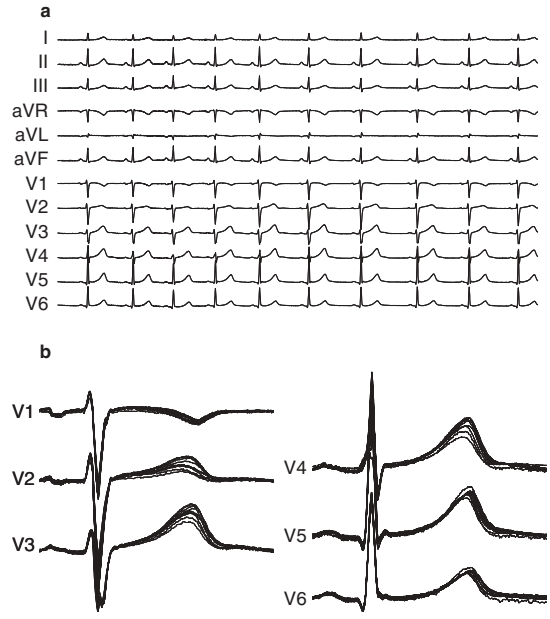

Fig. 2. (**a**) 12-lead ECG recorded in a healthy subject not taking any medication (note marked respiratory sinus arrhythmia). (**b**) Superimposition of all QRS-T complexes in pre-cordial leads. Note that while the QT interval is constant throughout the recording, the 'peakedness' and 'symmetry' of the T-waves substantially change from beat to beat.

different with every molecule but the modifications of the detailed channel electrophysiology might also be caused by other mechanisms, such as autonomic conditioning and CNS control (figure 3). This unfortunately means that observations made with one drug are not necessarily a good model for clinical experimentation with another compound. Moreover, because the mechanisms of the drug-unrelated changes are poorly understood, detailed separation of drug-induced and drug-unrelated effects is not only difficult but practically impossible at present. To some extent, this also applies to the QT interval duration but it seems that conditioning effects causing measurable QT interval changes have to be substantially more pronounced compared with those that might provoke subtle morphological changes.

This finally translates into a major obstacle that lies in the availability of suitable clinical data to pursue the goal of characterizing drug-induced changes in T-wave morphology. At present, perhaps most experience with drug-induced electrocardiographic changes exists with moxifloxacin because it is very frequently used as the positive control in the thorough QT studies. The drug has been reported to cause some distinct morphological patterns in the T-wave[14] but reproducibility and stability of these findings is still an open question. Moreover, because of this, it is far from obvious whether changes caused by one particular quinolone (mostly at one particular single dose of 400 mg) have any predictive meaning that could be used in investigations of other drugs.

Scientifically, it is of course pleasing that in this issue of *Drug Safety*, Graff et al.[15] report on T-wave morphological changes by d,l-sotalol (sotalol). Unfortunately, the same conceptual problems apply with generalizations of the reported findings. The electrophysiological actions of a powerful antiarrhythmic drug such as sotalol are of course unlike the actions of most non-antiarrhythmic drugs. Whether the reported morphological changes can be prospectively and meaningfully used with other compounds is clearly an open question. Also, with drugs that prolong QT interval as much as sotalol, the advantages of detailed morphological analysis can only be marginal. It is thus somewhat regrettable that Graff et al.[15] used rather simplistic data of QTc interval duration, such as correction for heart rate based on Fridericia's formula in spite of the known heart rate effects of the drug.

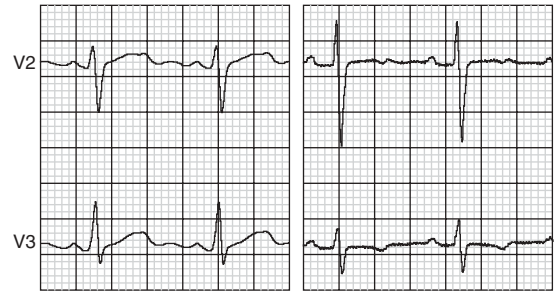

Fig. 3. ECG patterns of pre-cordial leads V2 and V3 recorded in two healthy subjects not taking any medication, during an episode of fear. Note markedly abnormal repolarization morphologies. Both before and after the episode of fear, the ECGs of these subjects were completely normal.

By treating the QTc interval data in a somewhat imprecise way, the authors gave the morphological assessment an undue advantage to some extent, which might be partially, if not entirely, responsible for the observed statistical differences.

The sotalol data used by Graff et al.[15] are unique and the Pharmacia team who allowed the widespread use of this dataset can only be thanked and congratulated for their openness in supporting this research field worldwide. Still, we must not forget that a substantial body of the recent reports on the electrocardiographic changes with sotalol[16,17] is coming from this single data source. While it would certainly be difficult, ethically and otherwise, to repeat the Pharmacia clinical experiment, some independent validations of the observations, not only those reported by Graff et al.,[15] are needed.

To a substantial extent, this is a general problem. Systematic examination of a large spectrum of drugs is needed, not only to persuade the regulatory agencies but also to obtain scientific confidence in the usefulness of clinical evaluation of drug-induced T-wave morphological changes, so that morphological characteristics common to different drugs and to different drug classes can be identified. Our knowledge of the drug-induced changes in QT interval duration is based on vast quantities of data, but to replicate this with modern digital ECG suitable for T-wave morphology processing and analysis is a task that can only be achieved as a truly massive collaborative endeavour by both the pharmaceutical industry and academia. Unfortunately, for reasons already mentioned in this commentary, the success of such a huge endeavour is far from guaranteed, while the expense involved, as well as clinical and ethical problems, would clearly be monumental. It is therefore possible, if not likely, that the bright future of the T-wave morphological analysis so clearly seen on the horizon a decade ago was just a pure mirage.

Naturally, this does not mean that studies like the one reported by Graff et al.[15] have no meaning. Perhaps, even if a universal drug testing strategy never emerges from the detailed understanding of the electrocardiographic morphology effects of different drugs, the knowledge gained might be helpful in the future development of both antiarrhythmic drugs and molecules of other pharmaceutical classes.

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