Factors Influencing Repolarization:
- Physiological Conditions and Factors to be Considered in Planning Clinical QT Studies -
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About sixteen years ago, clinical studies demonstrated a causal relationship between prolongation of cardiac repolarization and cardiac deaths by arrhythmias. At that time, it seemed an easy task to measure repolarization duration by QT, and to correct QT by the beat interval RR (=QTc). More recently, numerous studies have shown that there is no easy or straightforward assessment of QT duration, nor a clearcut link to risk of proarrhythmia and death. Furthermore, the definition of appropriate QT interval remains to be established, and its physiology elucidated.

QT interval describes the duration of depolarization of the heart ventricles, which is the duration of depolarization (QJ interval) plus repolarization (JTend interval). Thus impairment of depolarization (broadening of QRS complex) as well as blockade of repolarization can result in a QT prolongation.

Repolarization is influenced by a considerable number of factors. Imbalance of serum electrolytes is certainly one of the most common reasons for QT prolongation. It has been shown that food intake will seriously influence QT/QTc duration either. This relates to the influence by a shift in electrolytes, water, serum glucosis/insulin and fatty acids, which in turn impact on the regulation of the autonomic nervous system. Metabolic blocker agents like naringine from fruit juices are potent QT prologation agents.

Physical and mental activity may also influence repolarization duration, but primarily have an impact on heart rate and heart rate variability, which is reflected by the corrected QTc. Heart rate changes are short term reactions of the cardiovascular system to stimuli, while the repolarization follows in a delayed mode of action (QT/RR hysteresis). Endocrine factors are known to impact on repolarization, which is the major reason for a 30 ms longer QT time in females. This gender difference is directly related to the estrogen related remodelling of female heart. Genetic disposition of individuals determines a part of the susceptibility for drug induced QT prolongation, even for persons who are not carrier of a dangerous type of gene polymorphism, like short or long QT syndrome.

This presentation provides an outline of the most important factors, and relates them to the planning of clinical studies focussed on QT assessment. Considerations are made how to intervene in a study in case that side effects impact on repolarization, and how to include influential factors in the assessment of drug related QT effects.