Measurement Of QT Interval, Contractility (LV dp/dt\text{max}) And The Electro-Mechanical Window As Torsades De Pointes Risk-Markers In Anaesthetised Dogs, Minipigs And Guinea-Pigs

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It is increasingly recognized that QT prolongation alone is not a reliable biomarker for identifying the risk of Torsade de Pointes (TdP) in clinical or pre-clinical settings. Over the years several potentially more reliable risk-markers have been proposed (e.g. transmural dispersion, interventricular dispersion, QT instability, QT dispersion). Although some of these risk-markers seem useful in certain pre-clinical models, measurement of these markers in the clinic is invasive and time-consuming. Furthermore, these risk-markers only take into account the electrical aspect of a heartbeat.

To investigate both the electrical and mechanical aspects of the heart, we measured the QT interval, the left ventricular contractility (LV dp/dt\text{max}) and the Electro-Mechanical window (EMw) in three species after I\text{Ks}-blockade (JNJ 303) alone, and in combination with beta adrenergic stimulation (isoproterenol). The EMw was calculated as the difference between QLVP\text{end} (measured from the onset of the QRS complex to the end of the LVP signal) and QT interval (measured from the onset of the QRS complex to the end of the T wave).

In all three models; the fentanyl/etomidate anaesthetised beagle (FEAB) dog (n = 4), the fentanyl/etomidate anaesthetised Göttingen (FEAG) minipig (n = 4) and the pentobarbital anaesthetised Dunkin-Hartley (PADH) guinea-pig (n = 7), JNJ 303 induced major QT prolongations (+187%, +76% and +43%, respectively), but TdP was only elicited in the FEAB dog (50% spontaneously and up to 100% after beta adrenergic stimulation).

After comparison of the three models, we noted that in the FEAB dog, JNJ 303 (C\text{max} = 6360 ng/ml) induced a QT prolongation (+476 ms), enhanced LV contraction (+96%) and shortened QLVP\text{end} (-18 ms). This changed the positive EMw (+70 ms) to a large negative EMw (-425 ms). Unlike the FEAB dog, in the FEAG minipig, we observed no major increase in LV contraction (+11%). Despite the large QT prolongation (+292 ms), no large negative EMw (-18 ms) was observed, because the QLVP\text{end} was also prolonged (+153 ms). In this model, TdPs were not induced after JNJ 303 (C\text{max} = 8915 ng/ml), even after beta adrenergic stimulation. In the PADH guinea-pig model, the QT interval was also prolonged (+80 ms), but LV contraction was not greatly increased (+20%), QLVP\text{end} was prolonged (+20 ms) and no large negative EMw was observed (-28 ms) after JNJ 303 (C\text{max} = 20200 ng/ml). Also in this model, TdP were not observed and could not be induced after beta adrenergic stimulation.

We conclude that not only disturbances in the electrical events of the heart (e.g. QT prolongation), but also the mechanical events (e.g. contractility), and their relationship, must be taken into account when evaluating the arrhythmogenic liability of new entities. We introduced the EMw as a parameter describing the relationship between these two aspects of the heartbeat, and demonstrated that a change in the relationship between these two events (i.e., a large negative EMw) is a prerequisite in the induction of TdP after I\text{Ks} blockade.