

The electro-mechanical window in anaesthetized guinea-pigs: a new marker for TdP risk screening

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Introduction

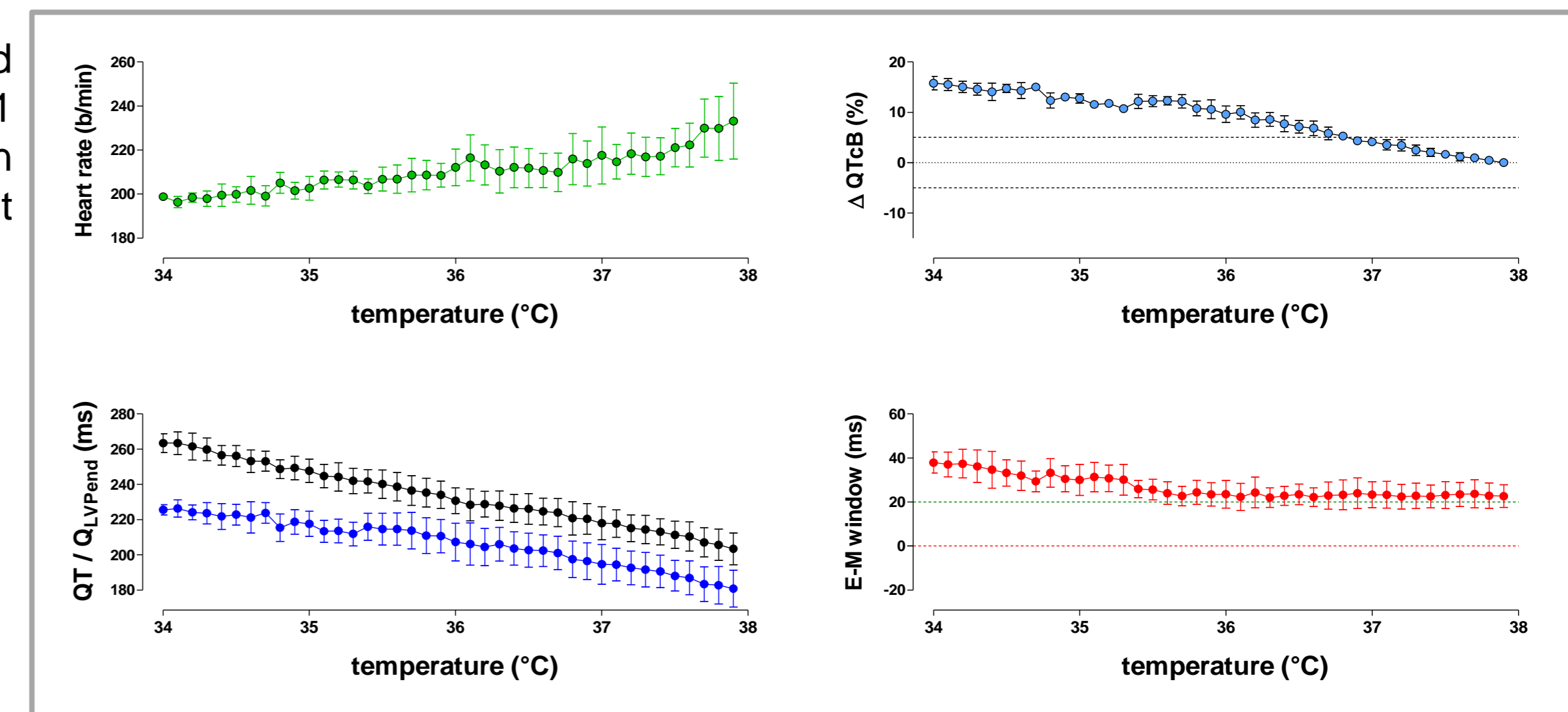
QT prolongation is commonly used as a surrogate marker for the pro-arrhythmic activity of non-cardiovascular drugs. However, it is increasingly recognized that QT prolongation alone is not a reliable marker for identifying the risk of Torsade de Pointes (TdP) in clinical or pre-clinical settings. Over the years several potentially more reliable risk markers have been proposed (e.g. transmural dispersion, QT instability, QT dispersion, triangulation of the AP). Recently, a negative electro-mechanical (E-M) window has been proposed as additional risk marker for TdP in a canine LQT1 model by van der Linde et al. The current work was aimed at explore the E-M window in anaesthetized guinea-pigs as potential screening marker for TdP risk in humans.

Methods

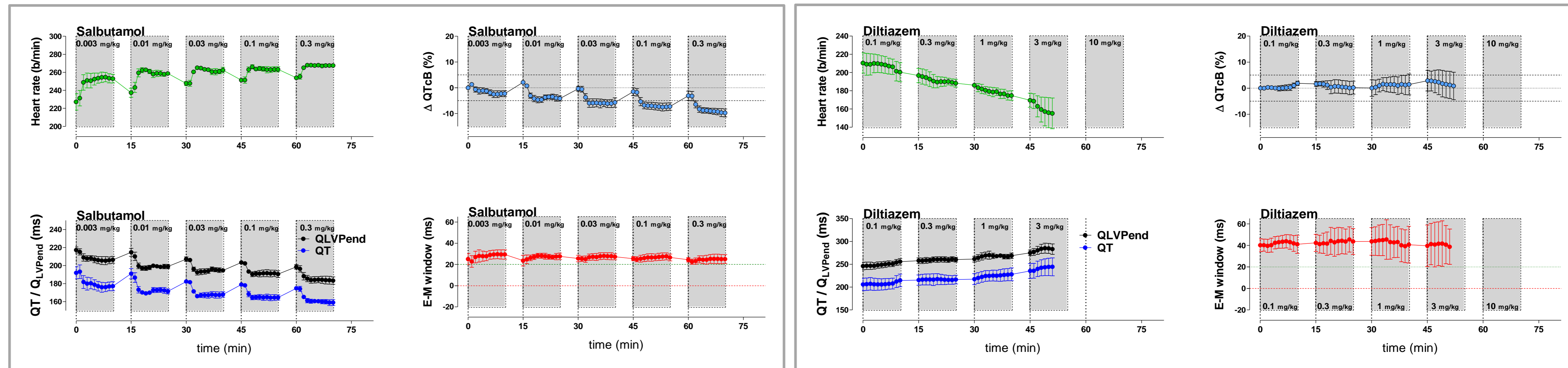
The E-M window, defined as the temporal dispersion of the duration of the electrical and mechanical systole (E-M window = $QLVP_{end} - QT$), was automatically measured (EMKA software) in anaesthetized and instrumented guinea-pigs. First the influence of changes in body temperature (rectal probe) and changes in heart rate on the E-M window were assessed. Secondly, the effects of various clinical reference drugs on the E-M window (and on the QTcB interval) were evaluated.

1. Effect of changes in body temperature on the E-M window

Cooling (heating pad switched off) of anaesthetized guinea-pigs from 38°C to 34°C induced a decrease of the heart rate and resulted in an increase of the QTcB interval (14.6 ms per 1 °C). The E-M window remained fairly constant despite the temperature decline; and even slightly increased below 35.5 °C. Graphs show mean and s.e.mean of 3 different experiments.

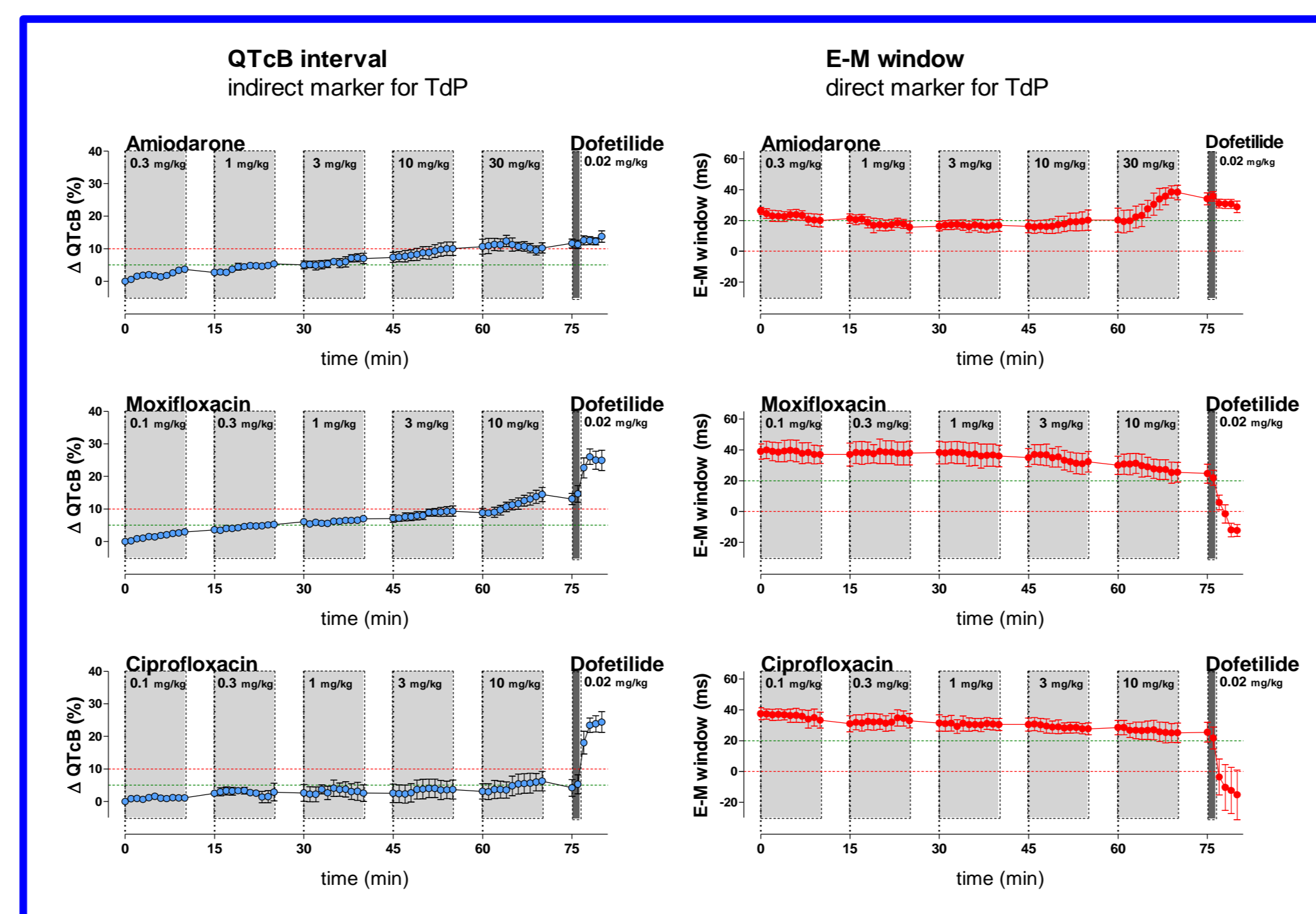
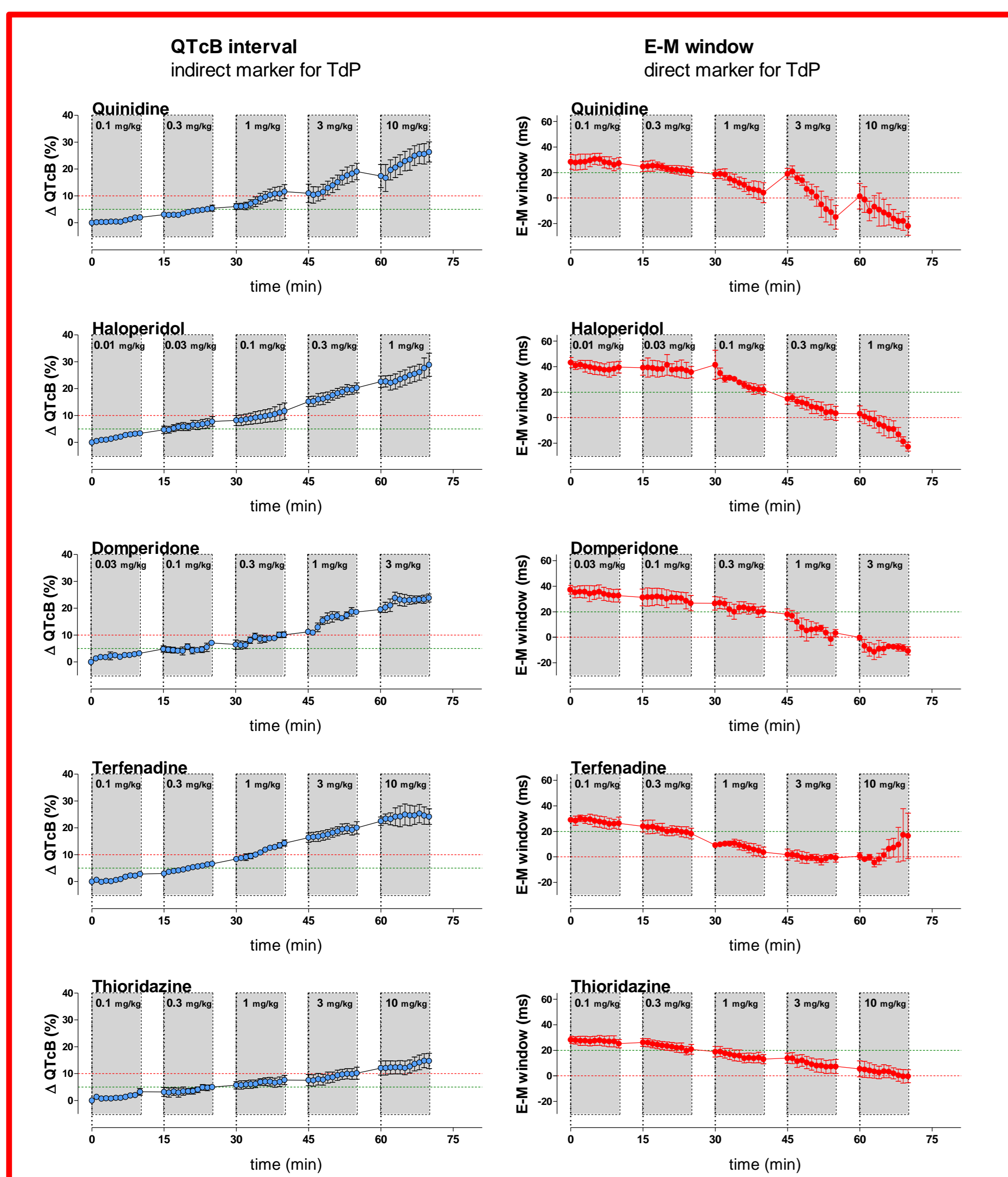


2. Effect of changes in heart rate on the E-M window



Salbutamol and diltiazem respectively drastically increased and decreased the heart rate. In contrast to the QTcB interval, the E-M window was minimally affected by drug-induced changes in heart rate. Graphs show mean and s.e.mean; n=5 (salbutamol); n=4 (diltiazem).

3. Validation with clinical reference drugs: the E-M window versus the QTcB interval

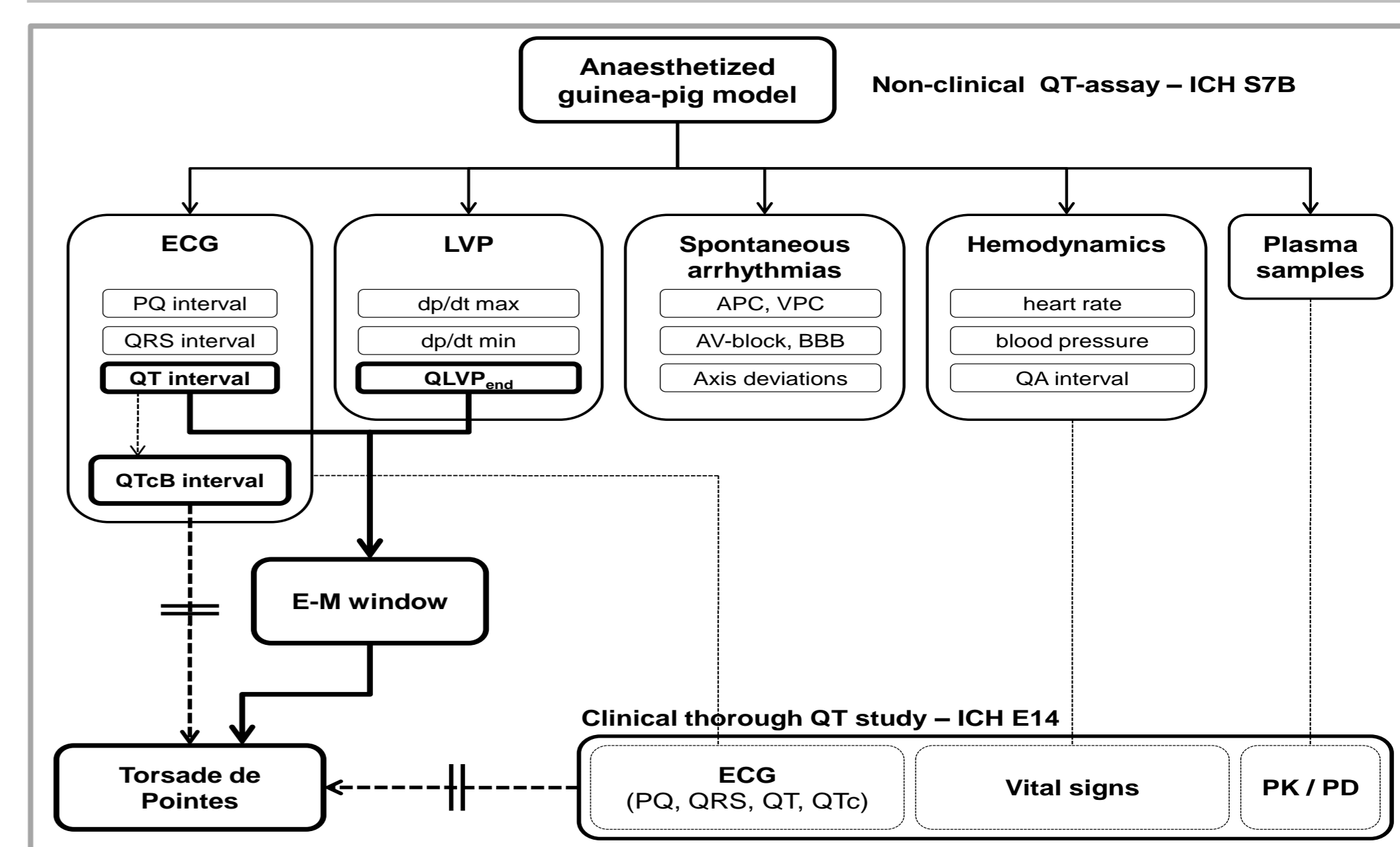


Clinical reference drugs with documented TdP liability (quinidine, dofetilide, haloperidol, terfenadine, domperidone and thioridazine) consistently inverted the E-M window, whereas compounds with no TdP risk in humans (salbutamol and diltiazem) failed to affect the E-M window. Interestingly, drugs with documented clinical QT prolongation, but with low(er) risk for TdP (ciprofloxacin, moxifloxacin and amiodarone) did not decrease the E-M window. The highest dose of amiodarone even increased the E-M window and prevented the induction of a negative E-M window by dofetilide. Graphs show mean and s.e.mean; n=3 (haloperidol); n=4 (quinidine, domperidone, terfenadine, vehicle, diltiazem, amiodarone, moxifloxacin and ciprofloxacin); n=5 (thioridazine, salbutamol).

Conclusions

- Automated measurements of the electro-mechanical (E-M) window in anaesthetized guinea-pigs are feasible and reproducible.
- The E-M window is a robust marker, minimally affected by changes in heart rate or body temperature.
- Negative E-M windows were consistently observed with drugs with high TdP risk, but not with drugs with no or low TdP risk.

These results suggest the electro-mechanical (E-M) window in anaesthetized guinea-pigs is a predictive risk marker for TdP in man.



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