Accurate detection of ECG intervals in anaesthetized guinea-pigs: man *versus* machine

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Introduction

Evaluation of the electrophysiological effects of new chemical entities on the electrocardiogram (ECG) is a paramount regulatory requirement. The QT interval represents the ventricular repolarization time and prolongation of the QT interval is associated with an increased risk of polymorphic ventricular arrhythmia.
Recently, drug-related effects on the PQ and QRS interval have also raised safety concerns.

Therefore the accurate measurement of QT, PQ and QRS intervals in pre-clinical cardiovascular safety testing is clearly important in the reliable detection of the associated risk.

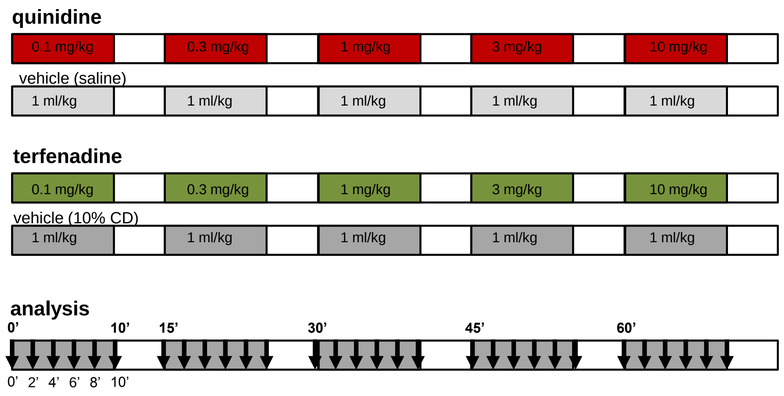
Manual analysis of ECG data is considered to provide most accurate read-out, but is time-consuming and requires well-trained ECG experts.

Establishment of an automated ECG analysis would be most helpful in reducing time, increasing the number of observations and limiting subjectivity.

The aim of this study was to compare the outcome of manual *versus* automated ECG analysis on efficiency and accuracy in anaesthetized guinea-pigs.

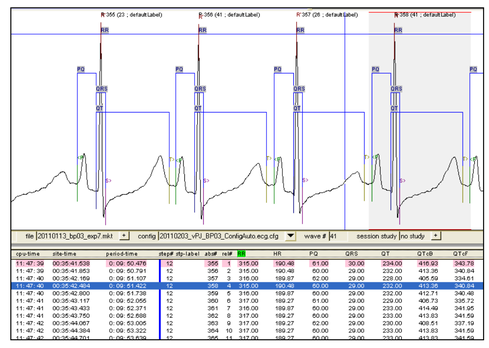
Methods

The data of 2 clinical reference compounds (quinidine, terfenadine, and the respective vehicle groups; total of 16 animals, n=4 per treatment group) were analyzed using two different approaches: manual review based on overlaying of consecutive beats *versus* automated analysis of individual complexes. The automated analysis used a shape recognition algorithm (EMKA Technologies, ECGauto software) in combination with a user-defined ECG waveform library.
Female SPF Dunkin Hartley guinea-pigs were anaesthetized (sodium pentobarbital, 60 mg/kg, I.P.) and artificially ventilated (1 ml/kg, 60 x per min). Compound was administered intravenously via the jugular vein. Four stainless steel ECG-needles were placed for recording of lead I and lead II. Blood pressure was measured via an open-lumen catheter in the left carotid artery and a tip catheter (Millar SPR-249) was placed in the left ventricle for assessment of left ventricular pressure (LVP).



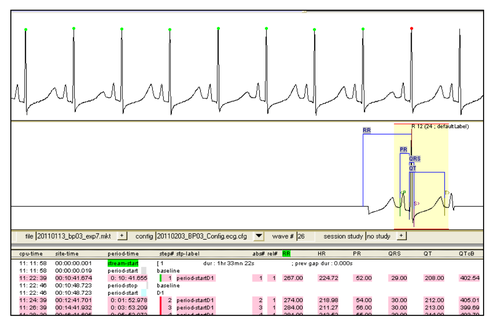
Automated ECG analysis

Automated analysis of **individual beats** was performed using EMKA Technologies software (ECGauto) that combines a shape-recognition algorithm with user defined ECG waveform libraries. The software used data sets of 20 individual beats and calculated a median for reporting.



Manual ECG analysis

Manual analysis was performed on an "**average-beat**" signal. Overlay plots of 10 consecutive beats were generated (aligned on the R-peak) and the ECG marks were positioned manually on the "overlay" ECG signal.



1. Individual Bland-Altman plots (pooled time points)

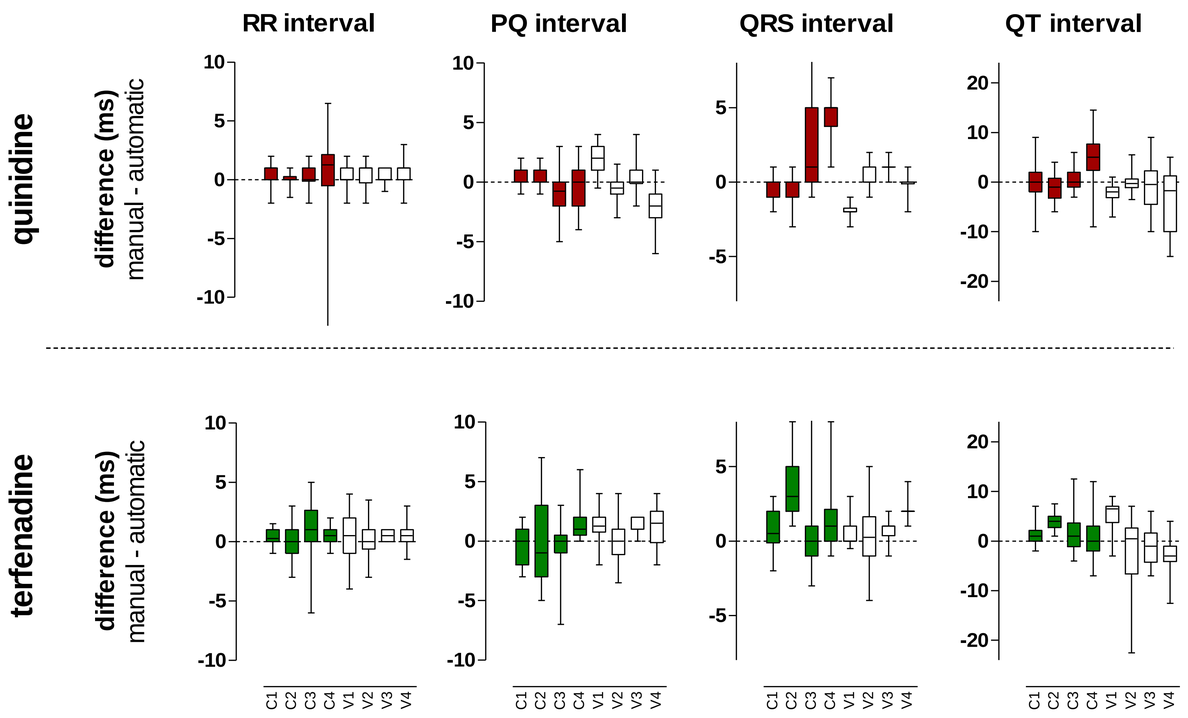


Figure 1: Graphs show comparisons of the manual *versus* automated method by Bland-Altman plots. Each box-plot represents the pooled time points of individual experiments (4 compound- and 4 vehicle-treated respectively). As expected, only minor differences for RR interval were observed (related to a small difference in duration of the reference period). Furthermore, for the PQ, QRS and QT intervals some degree of random variation between both methods was observed, but no pattern of systematic error could be identified.

2. Median delta values: man *versus* machine

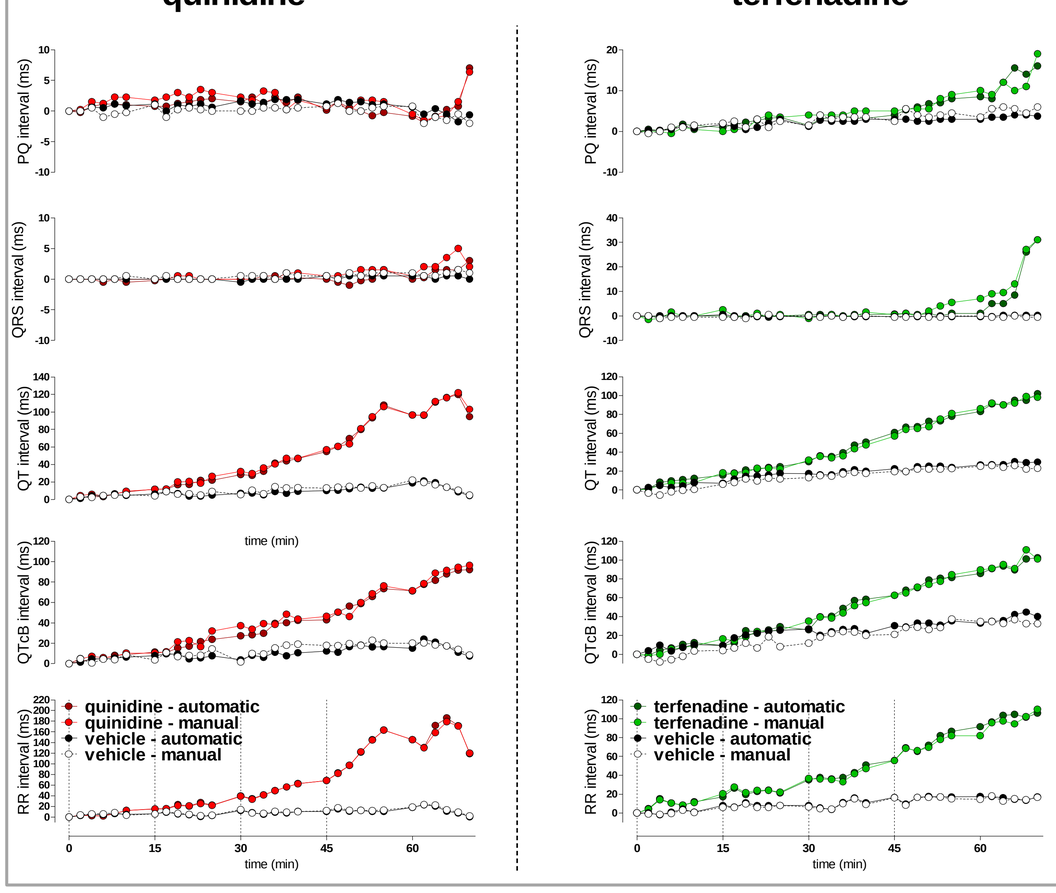


Figure 2: Graphs show median values per treatment group (n=4) assessed by manual or automated analysis. Both methods of analysis showed comparable outcome: quinidine markedly increased RR, QT and QTcB intervals, whereas tefenadine increased RR, PQ, QRS, QT and QTcB intervals.

3. Continuous automated analysis

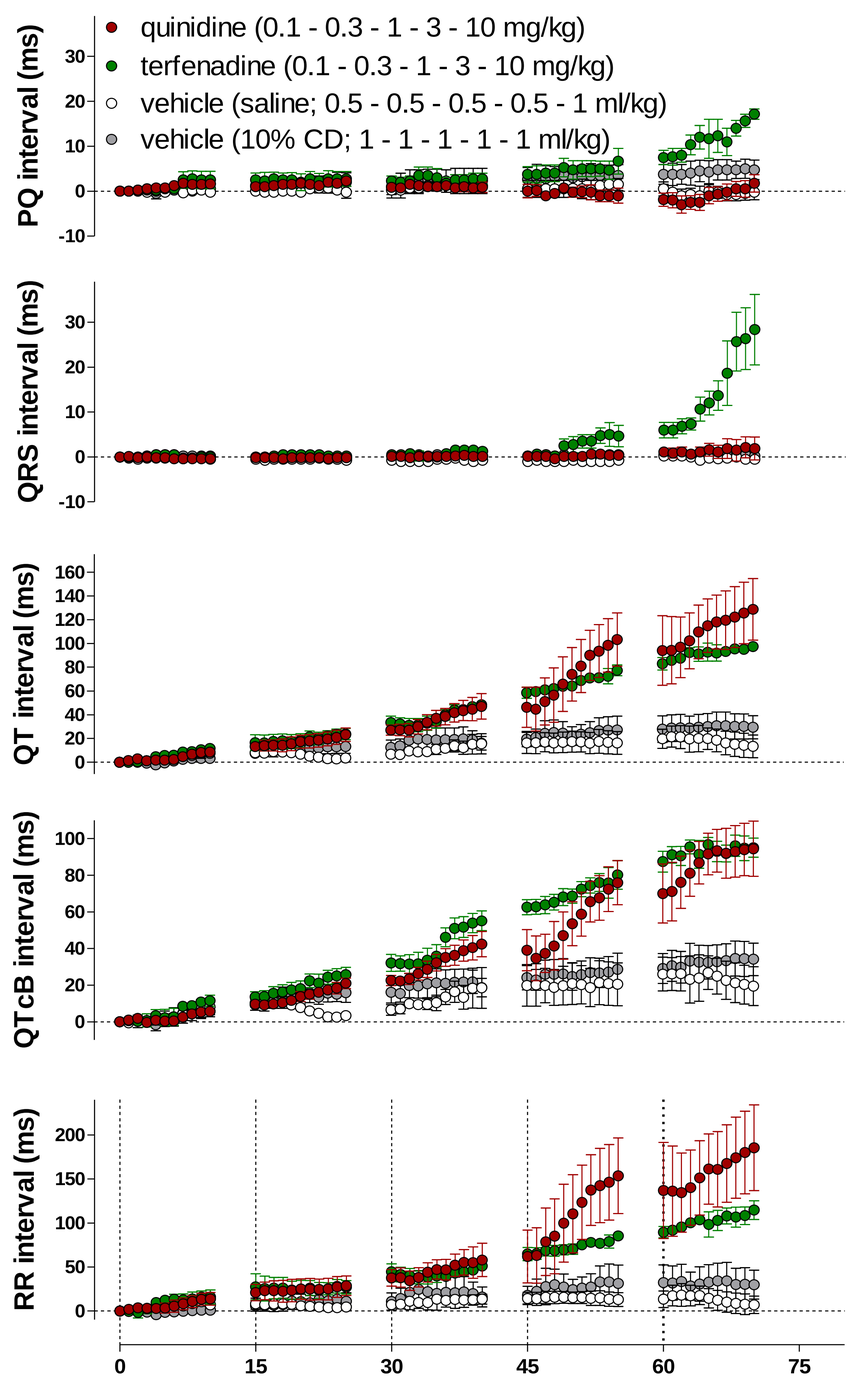


Figure 3: Final analysis of the validation studies was performed using automated detection of individual beats allowing for continuous monitoring of ECG intervals throughout the entire protocol. Results were reported as median values per minute. Graphs show mean and s.e.mean; n=4.

Conclusions

- Automated detection leads to **accurate, reproducible and time-efficient** analysis of ECG signals in anaesthetized guinea-pigs.
- Based on these results we advise **continuous automated analysis** of individual beats and report these as median values per minute.

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