

COMPARISON OF DIGITAL 12-LEAD ECG AND DIGITAL 12-LEAD HOLTER ECG RECORDINGS IN HEALTHY MALE SUBJECTS

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Introduction

Numerous publications on Thorough QT (TQT) studies display a wide range in ECG variability. Our meta-analysis study investigating the effects of (a) the baseline correction method (b) the design (c) the ECG recording method demonstrated that only the ECG recording method had a significant impact on data variability and it appears that digitally recorded 12-lead Standard bedside ECG are superior when compared to digital 12-lead Holter ECG recordings¹. TQT studies are currently the accepted method for investigating QTc interval changes of therapeutic and suprathreshold doses of new compounds². In addition, QT-RR hysteresis following changes in heart rate is an important factor in the variability of recorded ECG data and the outcome of QTc analysis³.

Aims

In this study, the variability of two commonly used digital ECG recording methods, 12-lead bedside ECG and 12-lead Holter ECG recorded simultaneously in the same subject, were compared and assessed.

Methods

This secondary analysis used the ECG data from a first into human study investigating the safety and tolerability of a new medicinal product in which bedside and 12-lead Holter recording methods were employed simultaneously.

Study Design

This was a prospective, single-centre, double-blind, placebo-controlled, ascending single oral dose, Phase 1 study in 34 healthy male subjects. One group participated in fed/fasted treatment periods.

Tolerability and safety was evaluated by adverse events (AEs), serious adverse events (SAEs), physical examination, body weight, vital signs, ECG, and clinical laboratory tests. At various time-points before and after the administration of study drug, venous blood samples were collected.

ECG measurement

During the baseline period on Day -1 and treatment period on Day 1, subjects were connected to a 24-hour Holter ECG device for simultaneous 12-lead ECG recording. The recorded data was used for retrospective 12-lead ECG snapshot extraction and analysis at protocol specified time-points. In addition, at the same time-points standard 12-lead ECGs were performed using MAC1200 machines.

Data Analysis and Statistical Methods

Prospective 12-lead ECG snapshot extraction was done at the same time-points as the standard ECG with retrospective ECG analysis by specialist cardiologists. This was to ensure that the ECG extracted from the continuous Holter data were suitable for the subsequent interval measurements. The bed-side ECG (Standard) was chosen from a triplicate at each time-point. We examined the differences in Standard Deviation (SD) for both data sets (Standard ECG and Holter ECG) using 1 ECG per time-matched time-point. This provided an opportunity to explore variability in data which owing to the simultaneous acquisition are attributable to experimental noise. Approximately 900 manually adjudicated ECGs were compared.

Subject Disposition

A total of 34 healthy male subjects were included in the study and were randomised to receive either active study drug or matching placebo, in five treatment periods (2 mg, 5 mg, 15 mg, 40 mg, and fasted/fed condition with 5 mg or matching placebo).

Of the 34 included subjects, 26 were Caucasian, 3 were Asian and 5 were Black/African American. The mean age was 25.7±4.8 years, the mean BMI ranged from 23.8 and 25.2 kg/m².

ECG Results

The results of interval measurements were only marginally different between the methods. The mean values for Standard ECGs showed slightly higher HR, slightly longer QT and similar (within millisecond) QTc values. When analysing the Standard deviations for PR, HR and QRS obtained from both methods, differences were observed (Figure 1 and Table 1). HR and PR showed more variability when recorded using Holter ECG compared to Standard ECG. QRS was the only parameter showing greater SD values for Standard ECG compared to Holter ECG. Standard deviations for QT, QTcB and QTcF Holter recordings showed up to 4 msec greater variability compared to Standard ECG recording (Figure 2 and Table 2).

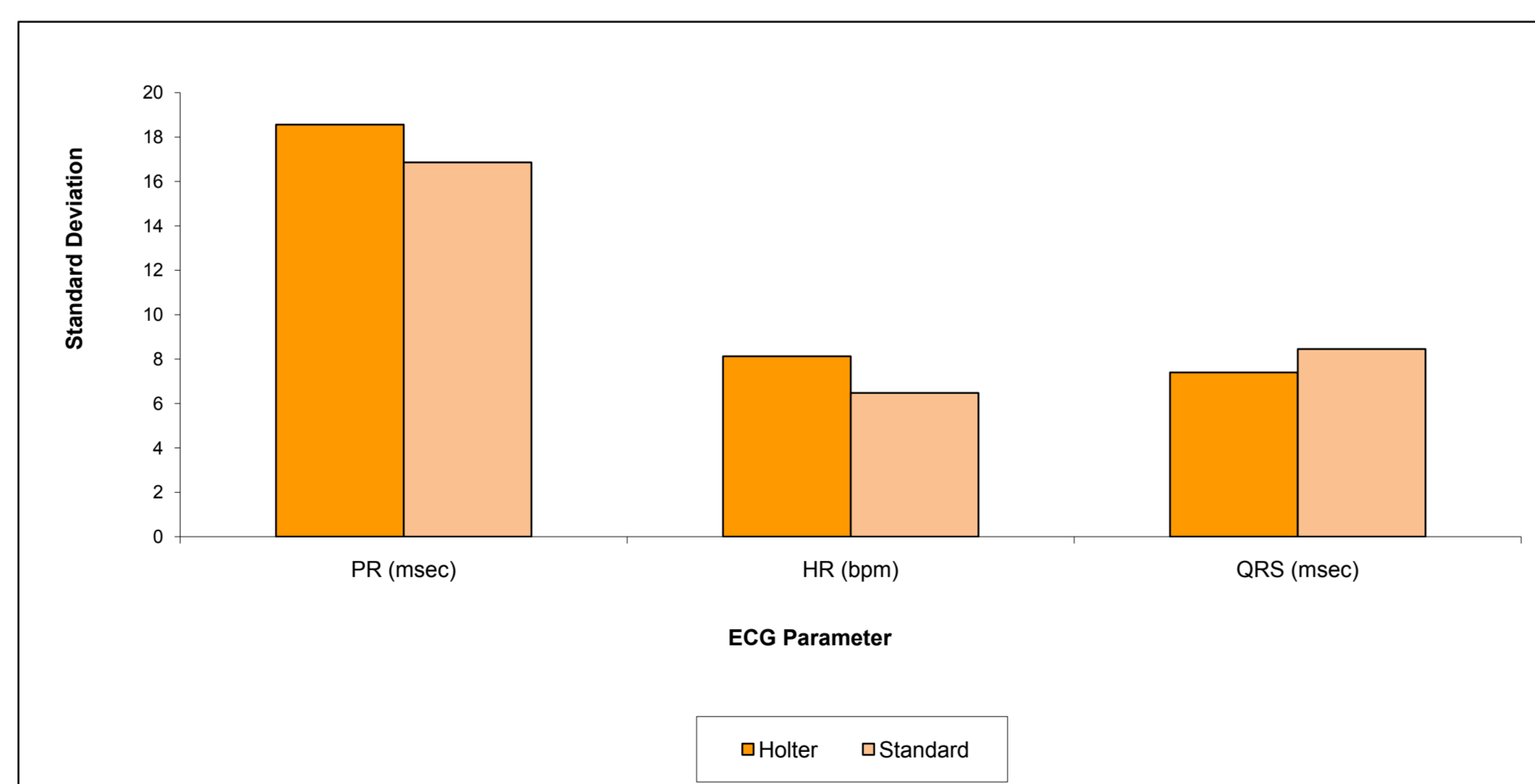


Figure 1 Comparison of Standard Deviation for PR, HR and QRS for Holter and Standard ECG data.

Parameter		Holter	Standard
PR (msec)	n	451	449
	mean	152.79	155.31
	SD	18.6	16.9
HR (bpm)	n	453	449
	mean	59.87	58.02
	SD	8.1	6.5
QRS (msec)	n	453	449
	mean	97.32	96.55
	SD	7.4	8.5

Table 1 Descriptive statistics of ECG parameters assessed by Standard and Holter method.

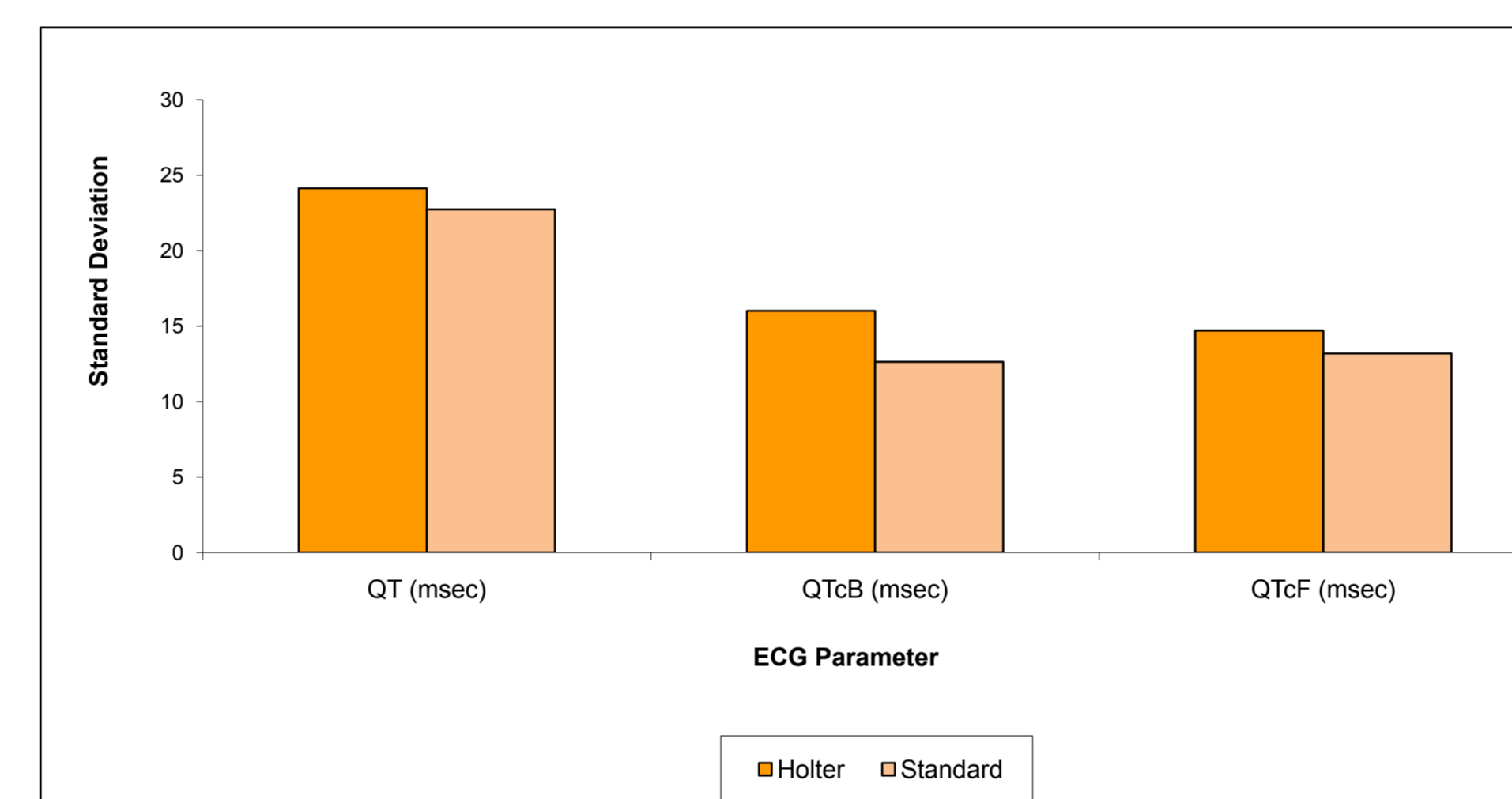


Figure 2 Comparison of Standard Deviation for QT, QTcB and QTcF for Holter and Standard ECG data.

Parameter		Holter	Standard
QT (msec)	n	453	449
	mean	399.65	404.03
	SD	24.2	22.7
QTcB (msec)	n	453	449
	mean	397.07	395.76
	SD	16	12.6
QTcF (msec)	n	453	449
	mean	397.74	398.42
	SD	14.7	13.2

Table 2 Descriptive statistics of ECG parameters assessed by Standard and Holter method.

Safety Results

There were no serious adverse events and no subject was withdrawn due to an adverse event.

Conclusions

The findings of this study are consistent with published data¹. The standard deviations for QT, QTcB and QTcF were higher for the data sets derived from Holter ECG traces. This demonstrates that digitally recorded Standard (12-lead bedside) ECGs are more accurate than digitally recorded Holter (12-lead) ECGs when using 10 second extraction with manual adjudication and that this effect is a combination of noise introduced during recording as well as at over-reading stage.

The QT-RR relationship is primarily influenced by heart rate with rapid changes in HR often leading to QT-RR hysteresis resulting in greater variability of QTc measurements^{3,4}. In addition, the autonomic nerve system is also thought to influence QT-RR which changes in response to sympathetic and vagal tone⁵.

It was noted that the differences between the two methods (Holter and Standard) observed in this study were smaller than those observed in literature which showed QTcF differences in SD of up to 5-10 msec¹. This is due to the fact that the recordings were made in the same subjects who were enrolled in the same study. The same ECG chest leads, same cardiologists and method of over-reading were used. Under these conditions, the Holter ECG data is improved compared to reported data, however, the challenge remains of selecting hysteresis free snapshots from Holter which even a top performing cardiologist may not always be able to do.

The advantage of using 12-lead Holter devices in TQT studies is that they provide a continuous data acquisition available for retrospective analyses such as e.g. safety reviews or beat to beat analysis. On the other hand, they make precise ECG acquisition more difficult leading to an increased variability due to QT/RR hysteresis^{1,4} which is unwanted noise. Automated measurement becomes a necessity to provide large enough sample sizes to overcome this experimental noise, although it is acknowledged that it is sometimes difficult in determining the end of the T wave which still limits the acceptability of automated ECG measurements.

Limitations of this study are that we only analysed a relatively small set of ECG. However, the findings do correspond with published data.

Overall, this study confirms that Holter ECG recorded in a controlled environment is less variable than that reported in literature. However, even if experimental noise is identical there is still a greater noise resulting from the difficulty in choosing ECG for manual adjudication.

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