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Influence of food intake on the QT and QT/RR relation

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Abstract

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Background

There are conflicting data on the influence of meal intake on the QT interval.

Methods

Ten healthy subjects were studied before and after a standardized breakfast and lunch with a sequence of supine resting, standing and exercise. Data collection was performed using a 12-lead Holter with semi-automated analysis. QT correction was performed using Fridericia (QTcF) correction formula and a subject-specific method based on individual QT/RR-regression (QTcI).

Results

Meal intake induced significant changes in HR ($p<0.001$), but not in QTcF ($p=0.512$) or QTcI ($p=0.739$). Postural analysis showed only significant differences in supine position for HR ($p=0.010$), not when standing or during exercise.

Conclusion

Food intake induced an increase in heart rate limited to supine position. Using QTcF and QTcI no QTc changes were found.

Keywords

QT interval, QT correction, Heart rate, Meal intake, Thorough QT studies

Highlights

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- Knowledge on meal induced QT interval changes is important in trials
- Meal intake induced a significant heart rate increase
- Adequate subject-specific and Fridericia QT correction remained unchanged

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Introduction

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A delay in ventricular repolarization, hence prolongation of the QT-interval, is a known risk for developing Torsades de Pointes (TdP), a potentially lethal ventricular arrhythmia[1]. Several drugs are associated with QT-prolongation and an increased risk of TdP[2]. Development of new drugs requires the execution of a thorough QT study (TQT) in accordance to the ICH Guideline E14 to rule out a possible QT prolonging effect of the compound[3]. The QT-interval is influenced by multiple physiological influences such as gender and autonomic activity.[4] Further, the QT interval adapts to heart rate changes in a process called hysteresis which acts with a certain delay in time.[4] Therefore a TQT study is designed with a strict set of rules concerning design and measurement to rule out these possible confounders.

Recent publications have indicated an influence of food intake on the QT-interval. Extreme fasting induced a QT prolongation which was corrected with refeeding[5], findings which were objectified in patients with anorexia nervosa[6]. However further reports were inconclusive and reported both QTc prolongation and shortening after food intake[7-9]. In the study by Hnatkova et al., inconsistent influences of food intake on the QT-interval were reported: after lunch there was a shortening of QT interval, but a prolongation was detected after dinner[10]. When moreover comparing the reproducibility of the QT interval under influence of moxifloxacin in this set-up, food ingestion was shown to have a poor power for inducing an effect on the QT-interval[11]. Recently, single ascending dose studies with exposure-response analysis in a limited number of subjects were suggested as potential replacement for complex and expensive TQT studies[12].

We aimed to study the effect of a standardized breakfast and lunch on the QT-interval using continuous 12-lead Holter monitoring in a limited population and as such relevant for future pharmacologic QTc investigations. In addition, whereas previous studies assessed supine rest only, our approach provided continuous monitoring during 4 identical sequences of 35 minutes before and after each meal, including a standardised period of standing and mild exercise, allowing us to perform a linear regression analysis of QT-RR profiles and investigating heart rate and QT changes in

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different positions.

Methods

Subjects

The study was approved by the ethical committee of the University Hospitals Leuven (s57404) and all subjects consented to the research protocol. The study included 10 healthy subjects without any cardiac history and free from any medication at the moment of investigation. An equal number of male and female subjects were included to compare gender related differences.

Study design

Subjects were fasting ten hours before the initiation of the study and bed-rest was recommended at 11 PM the day prior to the study. All subjects abstained from strenuous exercise and tobacco use at least ten hours before and from alcoholic beverages 24 hours before the study day. The food intake was standardized during the whole protocol with a fixed breakfast and lunch (table 1). For each meal a standard period of time for intake was provided (10 min for breakfast and 15 min for lunch), no food or beverages were to be consumed in between. In figure 1, a chronological scheme of the study protocol is depicted. Before and after each meal a monitoring sequence of 35 minutes was performed. Each monitoring sequence consisted of 10 minutes supine resting, 5 minutes of standing, a 6-minute hall-walk test and 14 minutes of supine resting. These monitoring sequences (S1: before breakfast, S2: after breakfast, S3: before lunch and S4: after lunch) were included in order to obtain sufficient variation in heart rate for acquiring an adequate individual QT-RR profile used for individualised rate-corrected QT interval and QT/RR slope analysis. Before the start of every sequence, a period of 10 minutes of supine resting was performed to minimize autonomic activity. During the period in between the two meals and sequences, further nominated as leisure time, subjects were free to perform light activity such as reading and walking.

ECG/ QT(c) assessment

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In all subjects a continuous 12-lead Holter monitoring was applied during the entire study protocol. The leads were placed as per the Mason-Likar modification in the standard places of the 12-lead system. The Holter devices were Spiderview Holters (Sorin Group, Milan, Italy) with a sampling rate of 200Hz. Electrocardiographic analysis was performed digitally using Synescope (Sorin). Recordings are automatically interpolated to an accuracy of 1ms (1000Hz) by the Synescope software. After manually controlled beat classification the software generates templates. A template is a 30 second averaged P-QRS-T complex based on all normal complexes in the 30-second interval. All artefacts, atrial and ventricular premature beats were excluded together with the subsequent normal complex. As such, a template complex represents a mean measurement over an interval of 30 seconds. The QT-interval was measured as the first deflection of the QRS complex until the end of the T-wave determined by the tangent method. The heart rate for every template is determined as the mean heart rate based on the automatically measured RR-intervals of every electrocardiographic cycle composing the template. Apart from RR interval, QRS duration and QT interval of every template were determined. All templates were reviewed for accuracy by two trained investigators (BS, BV) and manually adjusted if necessary. For standardized analysis all intervals were measured in lead I, based on availability of leads for analysis[13]. QT correction for heart rate was performed individually by the software, based on a linear regression analysis on all available QT-RR templates for every subject. Quality data of the QTcI correction are provided in supplement 1. The individual corrected QT interval, QTcI, is currently stated as the most accurate method for QT correction[14]. Additionally, Fridericia (QTcF) correction formula was used to make the comparison with population based correction methods.

Data analysis

Two different ways of data analysis were used. In the first analysis we used the data obtained during every 35 minutes sequence. For every subject the average HR, QTcF and QTcI interval and QT/RR slope of every sequence was calculated and used for statistical analysis. In the second analysis pre-

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specified time points were determined within every sequence: 40, 30 and 15 minutes before the beginning of each meal and 10, 20 and 30 minutes after the end of each meal (for each sequence during supine resting, standing and the 6 min hall-walk test, respectively). For every time point the available template closest to that time point was selected and measurements of the HR, QTcF and QTcI interval were used for statistical analysis. Since not every time point is recorded under the same conditions only comparison of time points under similar conditions is valid.

Because of interfering noise, one subject had incomplete data for the sequence analysis and two subjects for the time-point analysis.

Statistics

Continuous variables are presented as mean ± standard deviation, proportions as absolute number and percentages. All HR and corrected QT interval values of every subject were pooled per sequence or time point.

For the sequence analyses ANOVA statistics for repeated measurements were used to compare preselected sequences. The fasting sequence before breakfast (S1) was identified as baseline. Measurements after breakfast (S2) were compared with baseline (S2 versus S1) and after lunch (S4) versus baseline (S4 versus S1) or before lunch (S4 versus S3). The measurements before lunch were also compared with baseline (S3 versus S1) to test for significant diurnal changes in measurements. Bonferroni's multiple comparison test was applied for detecting statistically significant differences calculating both an overall p-value and an inter-sequence comparison approximated p-value reported. To detect gender differences an analysis overall and within sequences was performed comparing men and women using unpaired t-testing.

For the time point analysis, ANOVA statistics for repeated measurement were used to compare the time points in a same position within sequences, for example the HR in supine position between the different sequences. Bonferroni's multiple comparison test was applied for detecting statistically

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significant differences reporting an overall p-value of the analysis.

A p-value ≤0.05 was considered significant. All statistical analyses were performed using the Graphpad Instat Software version 3.0.

Results

Subject demographics and Holter recordings

We enrolled 10 healthy persons, 5 men and 5 women, without any cardiac history and not taking any medication. The age of the subjects varied from 24 to 60 years old with a mean age of 37.2 ± 14.2 years and an average BMI of 23.6 ± 3.6 kg/m². The average distance covered over all 6min hall-walk tests was 545.9 ± 44.9 meters. Quality data on the QT-RR templates are shown in Supplement 1. QTcI was derived from a mean of 552 ± 78 templates. The heart rate range spanned from a minimum of 51.4 ± 5.4 to a mean maximum of 88.2 ± 10.7 bpm. Since the protocol comprehended supine resting and exercise there was adequate heart rate changing. The mean correlation of QT/RR linear regression was 0.785 ± 0.050. QTcI/RR linear regression showed negligible remaining influence of heart rate on QTcI values. No other regression models were performed.

HR and QTc evolution after food intake

Results of the sequence analysis are summarized in table 2 and figure 2. The HR of each postprandial sequence was found to be higher than the sequence before meal intake. Overall HR differences were significant. However, QTcF (p=0.512) and QTcI (p=0.739) did not change significantly between the fasting and fed state. Comparing the above predefined sequences there was a postprandial increase in HR both after breakfast and lunch, but this rise in HR was significant only when comparing S4 with baseline (p≤0.01) and S3 (p≤0.001); there were no significant differences between the sequences before meals (S3 versus S1), showing a similar evolution of the HR over time during these periods.

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There were no significant differences for QTcF and QTcI.

The results of the time point analysis and statistics are summarized in table 3 and figure 3 and 4. It should be kept in mind that time point comparisons can only be made by analysing subjects in the same position or during comparable activity. We noted that the HR interval differed significantly between fasted and fed state in supine position (p=0.015), but not during standing or performing a 6 min hall-walk test. There were no significant differences analysing the QTcF and QTcI interval, although in supine position the QTc by either formula after the meals consistently tended to be increased compared to the fasting state.

Gender analysis

The population was equally divided by gender. The average age was 35.8 ± 14.2 years for male subjects and 38.6 ± 14.0 years for female subjects (p=0.786). Also, the BMI (25.3 ± 4.4 versus 21.9 ± 2.2 kg/m², p=0.161) and distance covered (561.7 ± 26.3 versus 530.1 ± 52.5 meters, p=0.263) did not differ significantly, for males and females respectively.

The baseline QTc interval was consistently longer in females for each formula but did not reach statistical significance (QTcF: 391 ± 14 ms versus 406± 20 ms, p=0.216 and QTcI: 392 ± 16 ms versus 400 ± 20 ms, p=0.528). As shown in figure 2 the HR was consistently higher in females. Analysis within a single sequence showed no significant gender differences for any of the parameters. Analysing all sequences together, 4 measurements for each subject, females had a significant higher HR (p=0.004) and longer QTcF (p=0.020) interval. There were no significant differences for QTcI (p=0.207).

Analysis of the QT-RR slopes of the separate sequences could not be performed due to interfering noise in several subjects and the low number of remaining available templates.

Discussion

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In the present study we were not able to reproduce a postprandial shortening of the QTcF and QTcI interval as was previously reported[9-11]. The only significant observation was a postprandial increase in heart rate in supine position, a well-known postprandial physiological phenomenon[15].

QT / RR correction

Garnett et al. have provided directives for optimal QTcI measurements[16]. There is no recommendation on the number of QT-RR templates individual correction should be based on, however with a mean of 552 ± 78 templates, corresponding to 4.6 hours recording, and a broad heart rate range we believe adequate correction could be performed (Supplement 1). Further, QTcI/RR linear regression shows a derived slope and correlation approximating zero. Time point measurements were performed at the end of stable body posture or continuous exercise when heart rate was stable. Despite the fact that hysteresis correction is recommended when the QT interval is subject to heart rate effects as of ± 2 beats per minutes in the preceding 2 minutes before measurement, hysteresis correction was not available in our analysis, but we believe adequate QT correction was performed because of the standardized protocol and adequate linear QT / RR.

Meal-induced QTc changes

Previous studies have observed a meal induced QTc prolongation using Bazett's correction formula[7, 9]. Because of the well-known limitations of the Bazett correction formula with significant overcorrection at higher heart rates, its use should be avoided in TQT studies or other studies requiring precise QT interval monitoring.[17] Published data using the Bazett correction formula should be interpreted with care. QT correction with the Fridericia formula does not show such increases in QTc with higher heart rates, because this formula is known to have a more accurate correction at higher heart rates[17]. In our study, the evolution of QTcF showed a similar profile to that of the QTcI. As for QTcI, no significant meal induced changes could be detected using the QTcF, although in supine position the QTc by either formula tended to be shorter in the fasting state than after the meal. This contrast to the findings of Taubel et al[9] reporting a shortening of the QTcF interval after

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food intake, but is in line with Hantkova et al[10], who observed inconsistent QTcI changes with shortening after lunch and prolongation after dinner. Taubel et al presented data of 55 subjects in a TQT study with moxifloxacin as positive control. The study was powered to detect differences of 12ms and the protocol contained a standardized breakfast. They observed an increase in heart rate of 9.4 bpm and a decrease of QTcF (-8.2 ms, 95% CI -6 - -10ms) and QTcI (-5.6ms, 95% CI -3 - -8ms) 2 to 3h after breakfast. They compare their results with an increase in heart rate and QTcB by Nagy et al[7] (n=11) and postprandial QTcF shortening of 11 ms by Bloomfield et al[18] (n=20). However, we must state that Nagy et al did only presented QTcB data based on manual measurements and mentioned that analysis with QTcF were similar[7]. Hence postprandial QTcF shortening was not confirmed. Further, Taubel et al did not describe extensively how QTcI was derived and as in our series no correction for hysteresis was performed.

Hnatkova et al presented data from a TQT study including 352 patients[10]. The QT intervals were corrected for heart rate based on individual QT-RR profiles and hysteresis with a well-described methodology. The study protocol included measurements after lunch and dinner (not breakfast) and the composition of the meals were standardized with a difference for daily caloric input between men and women. In women lunch and dinner led to a significant heart rate increase of 11.0 ± 4.0 and 6.8 ± 3.4 bpm, respectively. In men heart rate increased by 9.9 ± 3.4 and 4.5 ± 2.6 bpm, respectively. Results for QTcI were inconsistent with shortening after lunch by 2.9 ± 3.5 ms (not detectable in a substantial percentage of subjects) and 0.8 ± 3.6 ms and prolongation after dinner by 4.69 ± 3.66 ms and 3.53 ± 2.88 ms in women and men, respectively. The day-time profiles of intra-subject changes were similar in males and females. Later, they showed that reproducibility of QTcI changes was far less than for heart rate ($p<0.001$)[11].

Previous study results are inconsistent and show discrepant postprandial QT changes, which could have been caused by divergent diurnal effects. This suggest that meal-induced effects are not as unequivocal as suggested by Taubel et al[9]. All presented studies had a different design with different

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meals being analysed and measured QTcI with different methods. Whether the standing manoeuvres and physical exercise could be an explanation for the absence of postprandial QTcI interval change is open to speculation. Possibly because of autonomic interferences on the QT interval position and exercise could mask the food induced effect, since subjects where supine, a possible trend to food induced effects was detected. Diurnal variation and reproducibility of the findings can only be investigated with standardized measurements and protocols. Concerning the meal composition adaption to a patient's body composition should be investigated since a standard meal for a 25 year old 60kg sedentary women and a 40 year old sportive 75kg man probably differs significantly.

The suggestion by Taubel et al. to incorporate a standardized meal as negative control to demonstrate assay sensitivity in TQT studies replacing a positive drug-provoked control cannot be considered final until this topic is investigated thoroughly. The IQ-CSRC study showed that exposure-response analysis can detect significant QT effects in a small study (therapy group n=9, placebo n=6) with healthy subjects[19]. Therefore it was proposed that TQT studies can be replaced by robust ECG monitoring with exposure-response analysis in single ascending dose studies[19, 20]. The failure to reproduce known significant gender differences in the QTc interval illustrates the limitations of studies with a limited number of subjects which is relevant for future pharmacologic QTc investigations. Exposure-response analysis can take potential confounders, such as meal-induced QT changes, into consideration and the IQ-CSRC protocol included standardized meals. However, further development and validation of single ascending dose studies with exposure-response analysis is required before it could replace ICH E14.

Postprandial heart rate changes

Studying the differences in postprandial heart rate changes between body position or exercise when compared to fasting, a significant increase was only observed in supine position. All studies reported above performed measurements in supine position. The increased heart rate can be explained by the haemodynamic changes induced by postprandial splanchnic vasodilation and a drop in the total

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peripheral vascular resistance causing a decline in arterial blood pressures[9]. This is immediately counteracted via the baroreceptor reflex by an increase in cardiac output, established by an acceleration of heart rate. Whether postprandial supine heart rate changes are a results of sympathetic stimulation[21] or vagal withdrawal[22] is unclear. Remarkably there were no significant postprandial heart rate changes in standing position or during continuous exercise, indicating that the rise in sympathetic tone which was observed earlier does not increase further after consuming a meal[23, 24]. During the protocol heart rate increased significantly from supine to standing ($p<0.001$), however QTcI did not show any changes ($p=0.854$). Whereas QTcF was shown to decrease significantly from supine to standing position as part of autonomic manoeuvres in other studies (Williams et al n=54, Berger et al n=29)[25, 26], this was not reproduced in our study ($p=0.239$).

Limitations

The main limitation of our study is the small sample size, which might have prevented us from detecting small but significant meal induced changes in the QT-interval. We however do believe that with the rigorous standardisation of the meals and activity a significant change should have been detectable using this sample size and a paired analysis. Also, in view of the suggested strategy for future pharmacologic QTc investigations the presented study yield important clinical value as all conditions potentially influencing the QTc interval should be known in detail.[20]

The monitoring period after lunch was short, allowing the observation of only short-term QT alterations after lunch. In other studies investigators had time-matched controls of each subject at their disposal, allowing to define a more robust fasted QTc value serving as a reference point. Because in our study subjects were investigated on only one study day, we could base the fasted control value of the QTc interval on only one fasting baseline measurement period.

During the study protocol there were no blood samples obtained. Hence, no association of blood glucose, potassium or other plasma levels at interest with the study findings could be investigated.

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Finally, the presented values were not corrected for QT-RR hysteresis because the necessary software was not available at our centre. Since significant heart rate changes were observed, studying QT-RR hysteresis and hysteresis corrected QT values in a similar protocol would be of major interest.

Conclusions

In the present study food intake induced a pronounced heart rate increase with matching QT shortening. After correcting the QT interval adequately for heart rate using an individual based method no food induced QTc changes were found.

Declarations of interest

There are no competing interests to declare.

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Figure legends

Figure 1: The exact points in time of breakfast and lunch and the monitoring sequences are depicted. The double bars refer to the leisure time period.

Figure 2: Significant differences compared to S1 are highlighted with *, compared to S3 with †. There were no significant differences by gender within sequences.

Figure 3: Significant differences within a position between the time points are highlighted with * ($p \leq 0.050$).

Figure 4: Significant difference within a position between the time points are highlighted with ° ($p \leq 0.010$).

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Table 1: Summary of the composition of the two different meals.

	Amount	**Energetic value**
Breakfast		
Two pure butter croissants	2x40g	2x172 kcal
Orange juice	200 mL	79 kcal
Coffee	200 mL	/
Yoghurt with 6% sugar	125g	87 kcal
Total		***510 kcal***
Lunch		
Industrial made macaroni	400g	616 kcal
Chocolate mousse	75g	132.75 kcal
Mineral water	500 mL	/
Total		***748.75 kcal***

Abbreviations:

g: gram; mL: milliliter; kcal: kilocalories

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Table 2: Results of HR, QTcF and QTcI interval analysis comparing sequences.

	S1	**S2**	**S3**	**S4**
HR (bpm)	63.6 ± 8.9	66.8 ± 7.1	61.6 ± 7.3	68.4 ± 7.8
Versus S1		ns	ns	**≤ 0.010**
Versus S3				**≤ 0.001**
QTcF (ms)	398 ± 18	398 ± 16	397 ± 18	399 ± 14
Versus S1		ns	ns	ns
Versus S3				ns
QTcI (ms)	395 ± 17	393 ± 17	396 ± 18	395 ± 17
Versus S1		ns	ns	ns
Versus S3				ns

Presented p-values are approximated p-values of repeated measurements ANOVA with Bonferonni's multiple comparison correction for predefined sequence comparisons of interest. The overall p-value is presented in the text.

Abbreviations:

S1: sequence 1 before breakfast, S2: sequence 2 after breakfast, S3: sequence 3 before lunch, S4: sequence 4 after lunch, HR: Heart rate, bpm: beats per minute, ms: milliseconds, QTcF: Fridericia corrected QT interval, QTcI: subject specific corrected QT interval.

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Table 3: The results of mean HR, QTcF and QTcI values for the time point analysis.

	Position	S1	S2	S3	S4	p-value
HR (bpm)	Supine	59.1 ± 8.3	63.6 ± 9.9	57.0 ± 9.7	63.8 ± 11.4	**0.015**
	Standing	67.2 ± 11.0	70.0 ± 9.1	69.0 ± 12.3	69.1 ± 9.8	0.723
	6m hwt	79.1 ± 13.3	81.2 ± 15.4	83.2 ± 22.9	85.5 ± 16.0	0.538
QTcF (ms)	Supine	383 ± 14	394 ± 22	385 ± 12	394 ± 10	0.123
	Standing	392 ± 16	395 ± 11	389 ± 19	393 ± 15	0.671
	6m hwt	394 ± 19	395 ± 23	395 ± 15	404 ± 13	0.343
QTcI (ms)	Supine	384 ± 15	391 ± 20	386 ± 14	393 ± 10	0.234
	Standing	388 ± 18	389 ± 14	384 ± 17	391 ± 16	0.350
	6m hwt	382 ± 20	382 ± 18	383 ± 20	386 ± 18	0.878

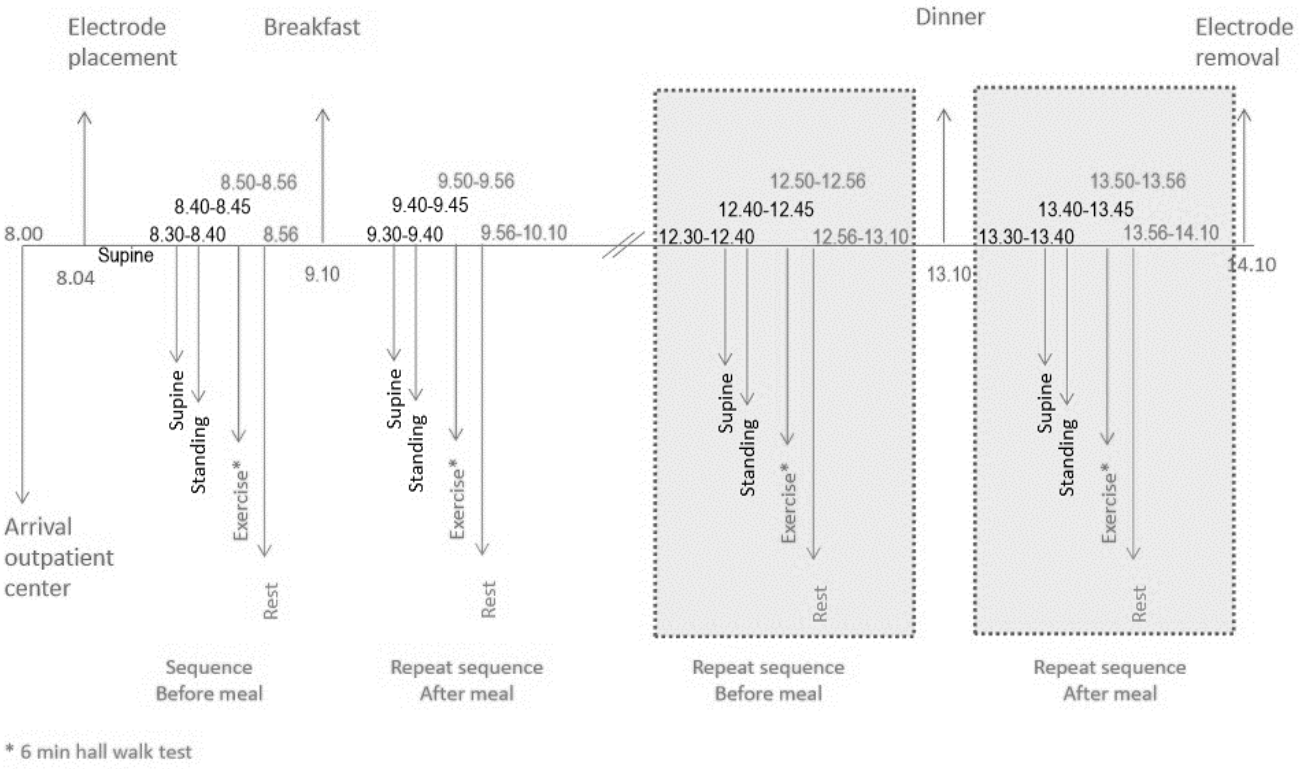
Presented p-values are overall p-values of repeated measurements ANOVA with Bonferonni's multiple comparison correction for comparison of all available time points in the same position.

Abbreviations:

S1: sequence 1 before breakfast, S2: sequence 2 after breakfast, S3: sequence 3 before lunch, S4: sequence 4 after lunch, HR: heart rate, bpm: beats per minute, ms: milliseconds, 6m hwt: 6 minutes hall-walk test, QTcF: Fridericia corrected QT interval, QTcI: subject specific corrected QT interval.

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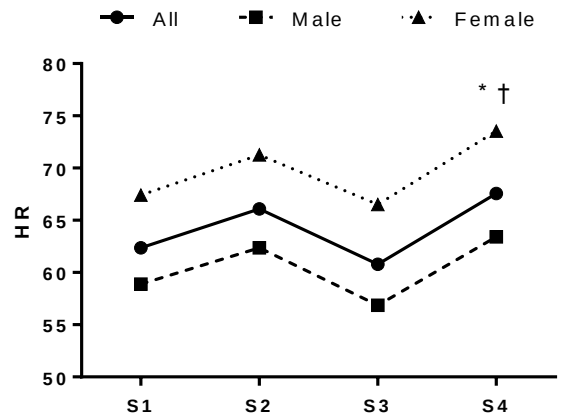
Figure 1: Overview of the study design.



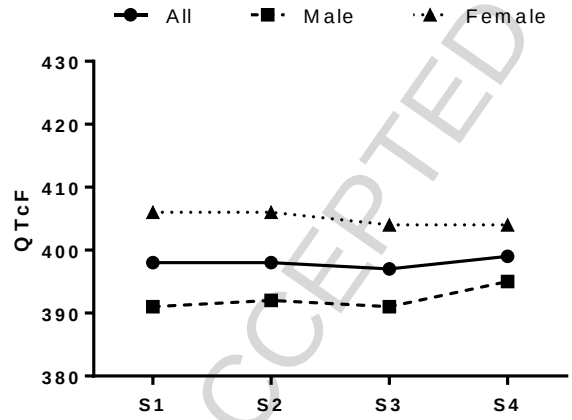
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Figure 2: Measurements plotted by sequence for all patients and by gender.

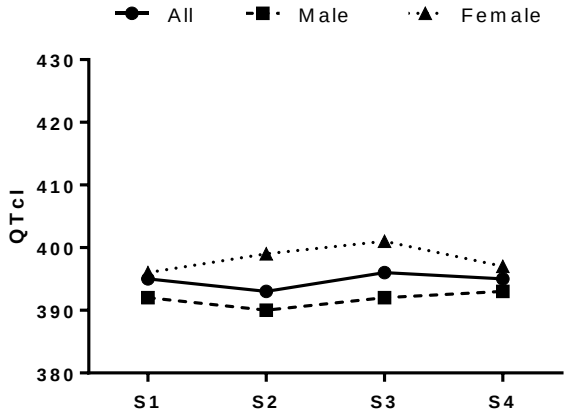
A. Heart rate



B. QTcF



C. QTcI

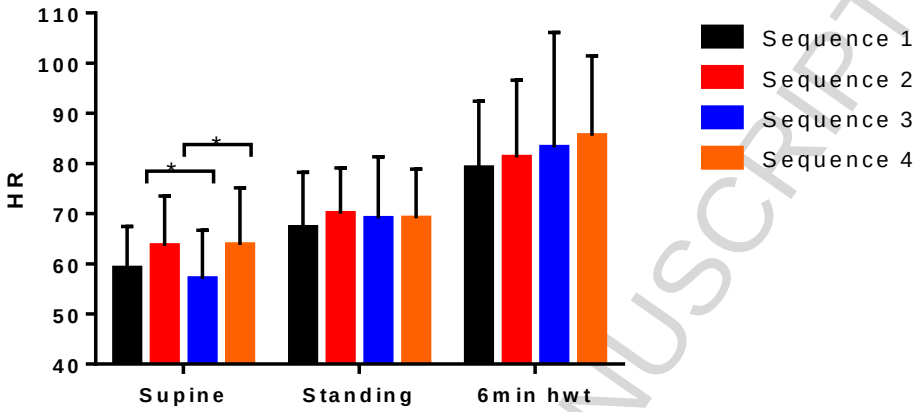


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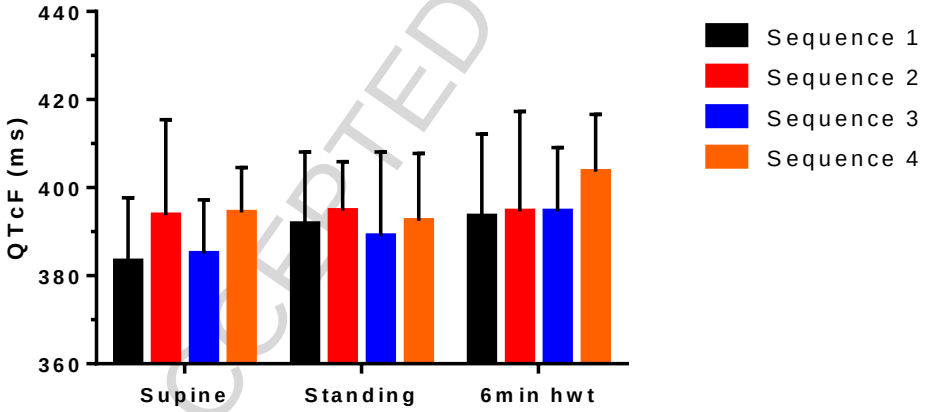
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Figure 3: Measurements plotted by time point and position for all patients.

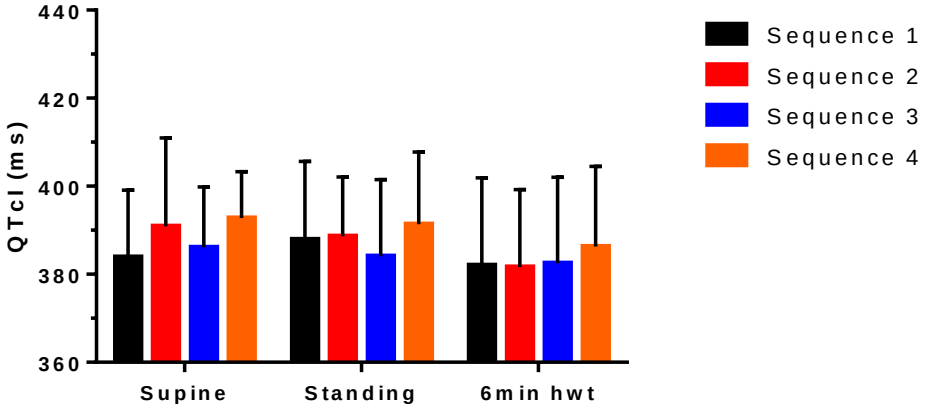
A. Heart rate



B. QTcF



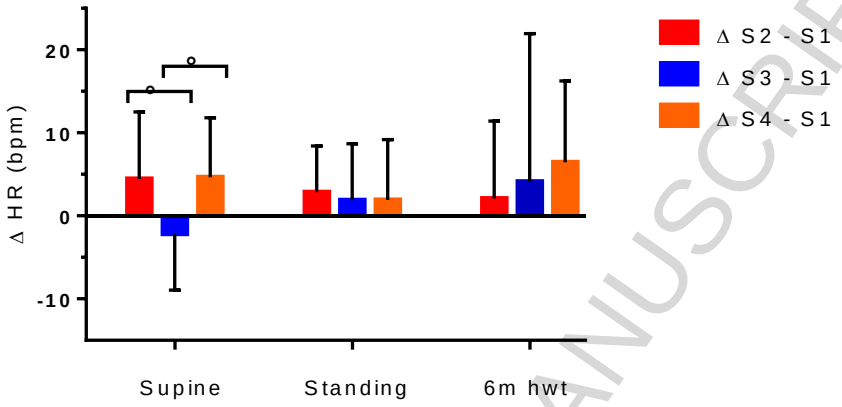
C. QTcI



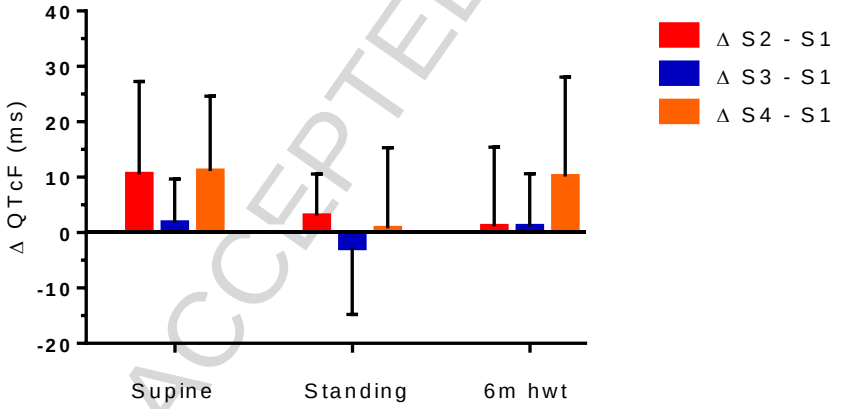
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Figure 4: The mean and standard deviation of the difference with baseline (S1) values plotted by time point and position for all patients.

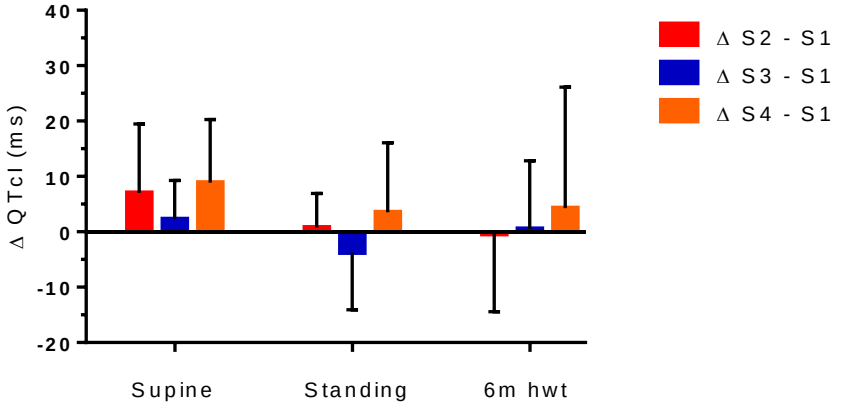
A. Heart rate



B. QTcF



C. QTcI



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Highlights

- Knowledge on meal induced QT interval changes is important in trials
- Meal intake induced a significant heart rate increase
- Adequate subject-specific and Fridericia QT correction remained unchanged

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