Usefulness of exercise test in the diagnosis of short QT syndrome

USEFULNESS OF EXERCISE TEST IN THE DIAGNOSIS OF SHORT QT SYNDROME

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ABSTRACT

Aims: Short QT Syndrome (SQTS) is a rare arrhythmogenic inherited heart disease. Diagnosis can be challenging in subjects with slightly shortened QT interval at ECG. In this study we compared the QT interval behavior during exercise in a cohort of SQTS patients with a control group, to evaluate the usefulness of exercise test in the diagnosis of SQTS.

Methods: Methods: Twenty-one SQTS patients and 20matched control subjects underwent an exercise test. QT interval was measured at different heart rates, at rest and during effort. The relation between QT interval and heart rate (HR) was evaluated by linear regression analysis according to the formula: $QT = \beta * HR + \alpha$, where β is the slope of the linear relation, and α is the intercept.

Results: Rest and peak exercise heart rates were not different in the 2 groups. SQTS patients showed lower QT intervals as compared to controls both at rest (276±27 ms *vs* 364±25 ms, $p<0.0001$) and at peak exercise (228±27 ms *vs* 245±26 ms, $p=0.05$), with a mean variation from rest to peak effort of 48±14 ms *vs* 120±20 ms ($p<0.0001$). Regression analysis of QT/HR relationship revealed a less steep slope for SQTS patients compared to the control group, never exceeding the value of -0.90 ms/beat/min (mean value -0.53±0.15 ms/beat/min *vs* -1.29±0.30 ms/beat/min, $p<0.0001$).

Conclusion: SQTS patients show a reduced adaptation of the QT interval to heart rate. Exercise test can be a useful tool in the diagnosis of SQTS.

Keywords: Short QT syndrome, exercise test, genetics.

CONDENSED ABSTRACT

Twenty-one SQTS patients and 20 matched control subjects underwent exercise test. Mean QT variation from rest to peak effort was 48±14 ms in SQTS *vs* 120±20 ms ($p<0.0001$). Regression analysis of QT/HR relationship revealed a less steep slope in SQTS patients. Exercise test is useful in the diagnosis of SQTS.

WHAT'S NEW

- Due to some overlapping of QT intervals between SQTS patients and general population, the detection of a short QT on a single ECG cannot distinguish all cases of SQTS from healthy individuals. Our data show a clear difference in QT adaptation to heart rate during exercise in SQTS patients as compared to controls. Regression analysis of QT/HR relationship revealed a less steep slope for SQTS patients compared to the control group, never exceeding the value of -0.90 ms/beat/min (mean value -0.53±0.15 ms/beat/min *vs* -1.29±0.30 ms/beat/min, $p<0.0001$). This value could be proposed as cut-off to help distinguishing affected subjects from those with slightly shortened QTc intervals at basal heart rates, but normal adaptation to increasing heart rates.
- The mean QT interval variation from rest to peak effort was 48±14 ms in SQTS patients *vs* 120±20 ms ($p<0.0001$) in controls. This may be a useful tool, easy to use in clinical practice.

INTRODUCTION

Short QT syndrome (SQTS) is a rare congenital ion channel disease with autosomal dominant inheritance, characterized by an abnormally short QT interval on the surface ECG and an increased susceptibility to life-threatening arrhythmias. Clinical presentation is heterogeneous; in the series of 53 patients published from our group in 2011 (1) over 60% of the subjects presented with symptoms: the most frequent was cardiac arrest (CA), which represented the first clinical manifestation in one third of the patients. Syncope or palpitations, often with evidence of atrial fibrillation (AF) represent other common clinical findings.

The diagnosis of SQTS is based on the detection of a constantly short QT interval on ECG; however, it is unclear which is the highest value of QT compatible with the syndrome. In the first described cases (2,3) the QTc interval never exceeded 300 ms; later, subjects with QTc intervals of 340 ms have been reported in the literature (4,5). More recently, a QTc interval up to 360 ms has been associated with aborted CA (1). From the analysis of several population studies that evaluated the QTc interval distribution in the general population, Viskin et al. suggested that values less than 360 ms in men and 370ms in women are relatively infrequent and thus should be considered as abnormally short (6). However, in those studies borderline or slightly shortened QT values were not associated with arrhythmic events. In contrast, Myamoto et al. recently analyzed a hospital-based population of 105,824 individuals, and reported two subjects with documented VF and syncope associated with QTc intervals of 332 and 355 ms; however, the patients also displayed, respectively, early repolarization and Brugada ECG pattern (7).

Due to the overlapping range of QT intervals in affected individuals and general population, it seems improbable that a single QTc value can distinguish all cases of SQTS from healthy individuals. This could make the diagnosis of SQTS sometimes difficult, while it is vitally important to distinguish between subjects with a borderline short QT interval and those with true short QT syndrome, due to the malignant potential of the disease.

In the first described SQTS cases a characteristic QT interval behavior during exercise was observed, with only a slight shortening during heart rate increase (3); later Wolpert et al reported that the QT peak/HR correlation was much weaker in three SQTS patients than in a control group (8).

The aim of this study was to evaluate the QT interval behavior during exercise in a cohort of SQTS patients, and to compare it with that of a control group from the general population, in order to evaluate the usefulness of exercise testing in the diagnosis of the syndrome.

METHODS

Study Population.

Twenty-one subjects with diagnosis of SQTS from 5 European Centers were included in the study (16 males, 76%). Inclusion criteria comprised QTc values below 360 ms (or 88% of QTp) in patients symptomatic for aborted SD or syncope of arrhythmic origin or with family history of SQTS. Patients with QTc values below 340 ms were included even if asymptomatic. Almost all the patients had a high probability of having SQTS according to the recently proposed Gollob Score (9), with a total score $\geq$ 4 points; only one patient resulted in a low probability of having SQTS with only 2 points (table 1).

Three subjects came to clinical observation with aborted CA, other 3 for a history of syncope and 6 for palpitations, in some cases with evidence of AF (table 1). Mean QTc interval at rest was 306±23 ms (range 268-345ms). In 8 subjects from four unrelated families a mutation in *KCNH2* gene was found, while genetic screening revealed no known mutation in genes encoding for potassium channels (KCNH2, KCNQ1, KCNJ2) in the others. The mean age at the time of exercise test was 31±15 years. Most of the subjects, 17, have been cited in previous studies (1,3-5).

Twenty healthy subjects with QTc values $\leq$ 390 ms and normal 12-lead ECG at rest (no evidence of ventricular hypertrophy, intraventricular conduction defects or repolarization phase

alterations), were recruited as control group. All of them were asymptomatic, without clinical evidence of cardiovascular disease. Mean QTc value was 375±12 ms (range 354-390 ms).

None was receiving any medication at the time of exercise test.

QT interval measurement and exercise protocol.

All subjects performed an exercise stress test: depending on the Center, treadmill (Bruce protocols) or bicycle ergometer were used. All the patients gave their informed written consent to the test. Twelve-lead ECG was monitored throughout the entire test and recorded at the end of each stage at a paper speed of 25 mm/sec; blood pressure was measured at appropriate intervals. QT intervals were measured manually from the precordial lead with the highest T wave amplitude (usually V2 or V3) by two independent examiners, both at rest and during effort up to peak exercise. Three intermediate HR values (HR25%-HR50%-HR75%) were obtained between rest and peak. As the study was mainly retrospective and the 5 HR points (HR at rest, HR25%-HR50%-HR75% and HR at peak) were not available for all the patients, a minimum of 3 HR points was required to include the test. During the recovery phase the QT interval was measured at HR similar to those considered during exercise; only HR75% and HR50% were considered in the analysis, as data at lower HRs were not available for most patients.

When the ECGs were available, the QT interval was measured both in supine and in upright position.

The QT interval was measured from the onset of the first QRS deflection to the end of the T wave according to the tangential method (10), as illustrated in figure 1.

Statistical analysis.

The relation between QT interval and heart rate was evaluated by linear regression analysis according to the formula: $QT=\beta*HR + \alpha$, where QT is the uncorrected QT interval in milliseconds, HR is the heart rate in beats/min, β is the slope of the linear relationship, and α is the intercept expressed in milliseconds. Regression was calculated from the data points acquired from rest to peak exercise as illustrated above.

We used multilevel mixed-effects linear regression models accounting for QT and HR time-dependent variables, with a random intercept and a random coefficient for modeling heterogeneity between individuals and an unstructured variance-covariance structure. All regression analysis were also multivariable and adjusted for age and sex. All analyses were performed using Stata version 12 and used 2-sided tests for significance at the 0.05 level, with 95% C.I..

RESULTS

ECG findings, at rest and during effort, as well as regression analysis results of the QT/HR relationship for affected subjects and controls are listed in table 2. In the exercise phase, in 7 patients and 5 control subjects data points for regression analysis were fewer than 5 (4 measurements in 11 subjects and 3 in one patient), due to the lack of recordings at all the desired heart rates.

There were no differences between the two groups in rest and peak effort heart rates. SQTS patients showed a lower adaptation of the QT interval at increasing heart rates: the mean variation of the QT interval from rest to peak effort was 48±14ms, compared to a mean of 120±20 ms in the control group, $p < 0.0001$ (figure 2, left). As a result, regression analysis of the QT/HR relationship revealed a less steep slope for SQTS patients as compared to controls (-0.53±0.15 vs -1.29±0.30, p value <0.0001), which never exceeded the value of -0.90ms/beat/min (range -0.33; -0.90) (figure 3), while in the control group the slope was always over -1.0ms/beat/min (range -1.05; -1.72). This holds true also for patient n° 20 (see table 1), who had reached a total of only 2 points in the Gollob's score, resulting in a low probability of having SQTS, but showed a slope of -0.74 ms/beat/min. When the analysis was repeated also considering the time from rest to peak HR, the slope for SQTS patients was -0.45±0.86 and for controls -1.27±0.06, $p<0.0001$.

Data of the recovery phase were available for 14 SQTS and 18 controls. The mean variation of the QT interval from peak effort to HR50% was 23±17 ms, compared to a mean of 43±20 ms in the control group, $p < 0.01$ (figure 2, right and figure 4). Also in this phase SQTS subjects displayed

a flatter QT/HR slope (mean value 0.50±0.19 vs 0.97±0.35, p <0.0001). When considering in the multilevel regression analysis the time from peak to HR50%, the slope for SQTS patients was 0.52 ±0.11 and for controls 1.14±0.12, p<0.0001.

The analysis was repeated excluding the eight SQTS patients with KCNH2 mutations, who were those with the shortest QT and QTc intervals, both during exercise (mean QT variation from rest to peak exercise 51±16 ms; mean slope -0.55± 0.14, p<0.0001) and in the recovery phase (mean QT variation from peak HR to HR50% 27±18 ms, mean slope 0.58±16, p<0.0001).

In a multilevel analysis controlled for age and sex, we found that age did not influence the QT/HR slope during exercise. In the SQTS group, female subjects exhibited steeper slopes than males (β =-0.58, 95%C.I.: -0.46, -0.70, versus β= -0.52, 95%C.I:-0.43, -0.60, p=0.02). To analyze whether *KCNH2* carriers and patients with unknown genotype had a different behavior, we repeated the analysis not considering the female subjects, as all of them had *KCNH2* mutation. Males with *KCNH2* mutation showed a flatter slope as compared to those with unknown genotype: in the first group β was – 0.36 (95% C.I. -0.25, -0.47) versus β =-0.55 in the second (95% C.I. -0.45, -0.62, p=0.02).

In our study we observed 6 patients with a history of cardiac arrest (n=3) or syncope (n=3). In a multilevel regression model adjusted also for age and sex, a previous occurrence of CA or syncope didn't show a significant influence on QT slope (p=0.78).

In 10 SQTS patients in which rest ECGs were available both in supine and standing position, mean HR increased of 15±7 bpm, mean QT and QTc variation was -10±8 ms and 15±14 ms, respectively.

DISCUSSION

Several studies have analyzed the QT and QTc behavior during exercise test in healthy individuals from the general population. In 1996 Kligfield et al (11) observed that the unadjusted QT interval varies linearly with heart rate, and for this reason the determination of QT/HR slope,

quantifying the QT adaptation to HR, could represent an easy method of representing their relationship during exercise. In a paper by Magnano et al. the autonomic nervous system influence on repolarization was evaluated, investigating the relationship between HR and QT interval during exercise and during atropine or isoproterenol infusion (12). In these two studies the mean QT/HR slopes during exercise in control subjects from the general population were respectively -1.45±0.34 and-1.29±0.23 ms/beats/min in men and -1.74±0.32 and -1.43±0.21ms/beats/min in women.

In 1991 Vincent et al (13) reported abnormal QT responses to exercise in patients with type 1 LQTS as compared to normal subjects; Swan et al (14) observed that during the recovery phase after exercise the QT/HR slopes were steeper in children with Long QT syndrome than in controls. It has also been reported that the adaptation of the QT interval is different in the three major LQTS subtypes, suggesting that it could be helpful in predicting and directing the genetic testing in affected patients (15), and in distinguishing asymptomatic LQTS mutation carriers with no or borderline QT lengthening from normal subjects (16,17).

Isolated reports have reported the behavior of the QT interval during exercise in a limited number of SQTS cases. Wolpert et al. analyzed the rate dependence of the QT interval during exercise in three SQTS patients with a mutation in *KCNH2* gene and found a weak correlation between heart rate and QT peak interval. Moreover, they found that the administration of quinidine partially restored the heart rate dependence of the QT peak interval toward the range of adaptation reported for normal subjects (8). Antzelevitch et al. reported QT/HR slopes from -0.54 to -0.99 ms/beats/min in three subjects carrying a mutation in *CACNA1C* or *CACNB2b* genes, which are responsible for a mixed phenotype of Brugada pattern ECG and shorter than normal QT intervals (18). Sun et al. reported a similar behavior in two subjects with a novel mutation in the *KCNH2* gene, with QT/HR slopes of −0.55 and −0.74 ms/bpm (19).

Currently, the diagnosis of SQTS is based on the finding of a constantly short QT interval on 12 lead ECG. Our group in 2011 published the long-term follow-up of 53 SQTS patients (1). Inclusion criteria comprised a QTc interval ≤ 340 ms even in the absence of symptoms, or a QTc interval up

to 360 ms in association with a history of cardiac arrest or syncope of arrhythmic origin, or belonging to SQTS families. A scoring system based on electrocardiographic, clinical and genetic parameters has been shortly after proposed in order to define the probability of having SQTS (9). The analysis of the QT/HR relationship was not included in the variables considered in that study, due to the absence of validation of the above-mentioned observations in a large cohort of patients. In consideration of the known limitations of the Bazett's formula at heart rates > 100 bpm, during exercise the evaluation of the relationship between uncorrected QT values and HR seems preferable. Our data on 21 SQTS patients compared to controls show a clear difference in QT adaptation during exercise, because the QT interval in the affected subjects does not shorten as expected with increasing heart rate. As a consequence, the regression lines show that the QT intervals in the two groups come closer to each other at the highest HR (Figure 2A).

Although a less dynamic QT adaptation to heart rate has been observed also in healthy subjects (11), values of the QT/HR slope less than -0.9 ms/beat/min have not been reported. As a consequence, in subjects with QTc intervals between 340 and 360 ms, the presence of a QT/HR relationship slope under -0.9 ms/beat/min could help distinguish affected subjects from healthy individuals. Using this value as cut-off we were able to recognize a subject with short QT interval in several ECG recordings, that would have not been considered as affected based on Gollob's score, but who exhibited values of QT/HR relationship that, as far as we know, are not common in the general population.

Other findings in this study are that the QT/HR slope is significantly flatter in the subgroup with a *KCNH2* mutation, which shows the shortest QT intervals, as compared with the subgroup with unknown genotype. This analysis was performed only in male patients as all the female subjects had *KCNH2* mutation. The slope is steeper in female, as compared to male SQTS patients, similarly to what has been reported for normal subjects (11).

Also in the recovery phase the QT/HR slope is flatter in the SQTS patients than in the controls.

The response of the QT interval to brisk standing has been evaluated in subjects with LQTS (20), demonstrating an impaired adaptation of the QT to the acceleration of the HR. Our data suggest that also in SQTS the QT adaptation to standing is reduced, as compared to the values for a normal population reported by Viskin et al.

STUDY LIMITATIONS

Due to the mostly retrospective nature of this study, the exercise protocol was not standardized and the ECG data, especially during the recovery phase, were not complete for all patients, although sufficient for the analysis. The evaluation of the reproducibility of our observations is affected by the fact that most patients began a pharmacological treatment.

The preliminary observation of an altered response of QT interval to postural changes in SQTS patients needs to be further validated in a larger controlled study.

Conflict of interest:

None declared.

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FIGURE LEGENDS

Figure 1.

QT interval measurement according to the tangential method.

A. 12-lead ECG during stress test of a17 years old male patient with short QT syndrome. B. The QT interval was measured in lead V2 from the onset of the first QRS deflection to the end of the T wave according to the tangential method.

Figure 2.

HR/QT relationship in SQTS (blue line) and controls (red line) during exercise (left) and during recovery (right).

SQTS patients showed a lower adaptation of the QT interval at increasing heart rates. QT points represent the mean values at 25%, 50%, 75% and 100% of the HR range from baseline to peak exercise and back to 75% and 50% of the HR during the recovery phase.

Bars indicate 95% Confidence Intervals. HR= heart rate.

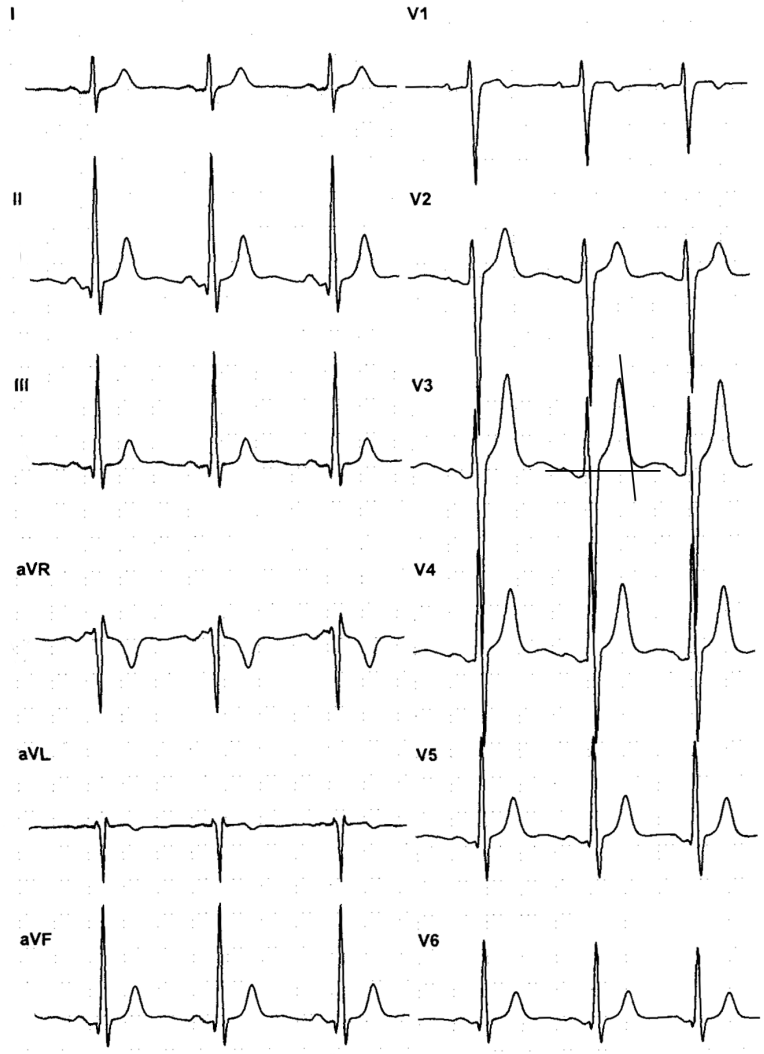
Figure 3. Regression analysis between QT interval and heart rate during exercise in SQTS patients (3A) as compared to the control group (3B).

Values on the vertical axis represent the predicted QT following the relation $QT=\beta*HR + \alpha$. HR= heart rate.

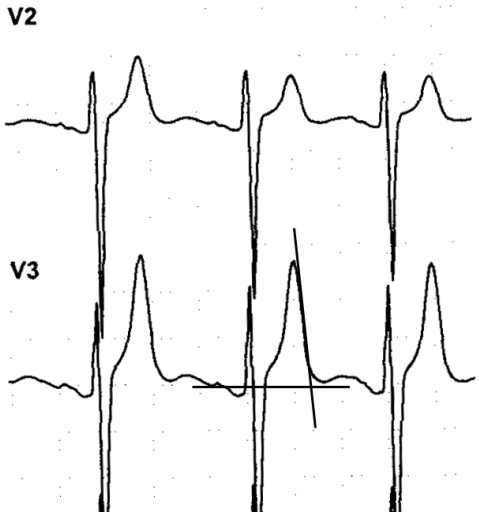
Figure 4. Regression analysis between QT interval and heart rate during recovery in SQTS patients (4A) as compared to the control group (4B).

Values on the vertical axis represent the predicted QT following the relation $QT=\beta*HR + \alpha$. HR= heart rate.

Figure 1.

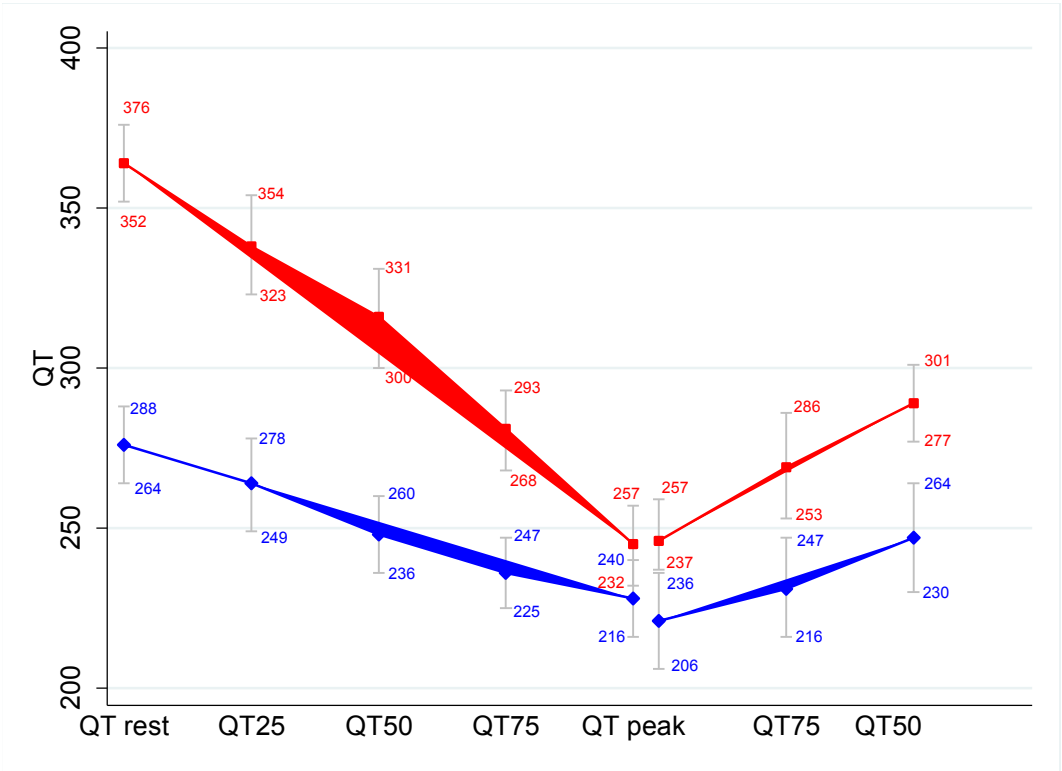


A.



B.

Figure 2.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QT rest
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QT peak
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QT50

Figure 3A.

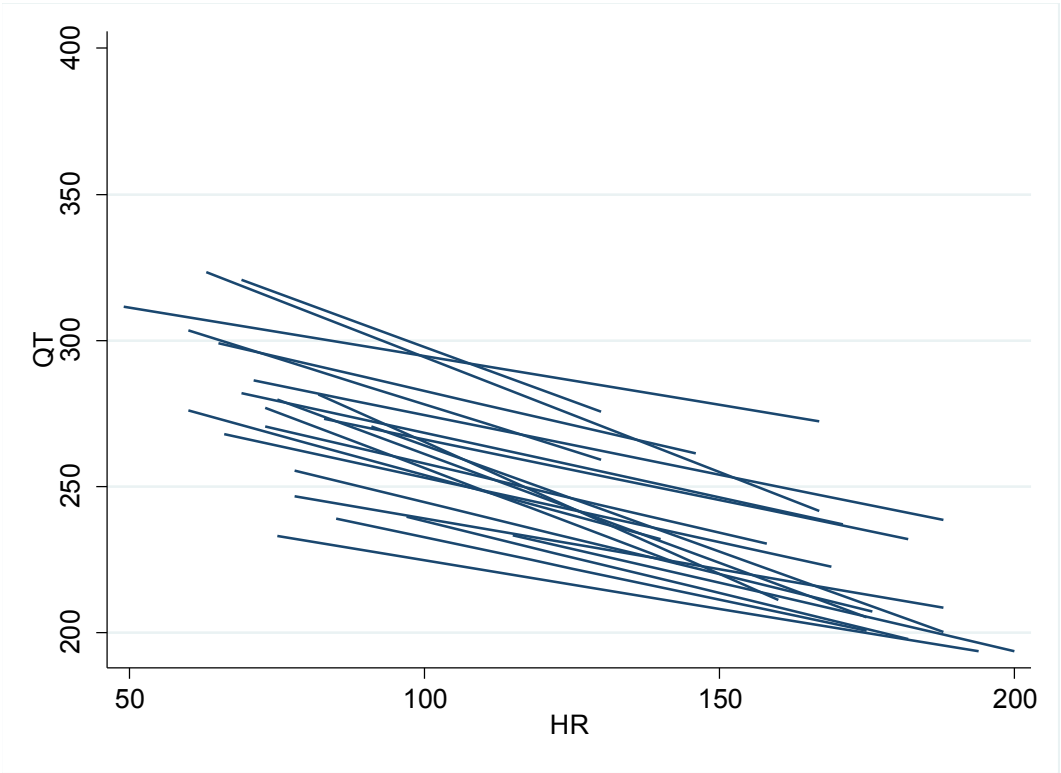

Figure 3B.

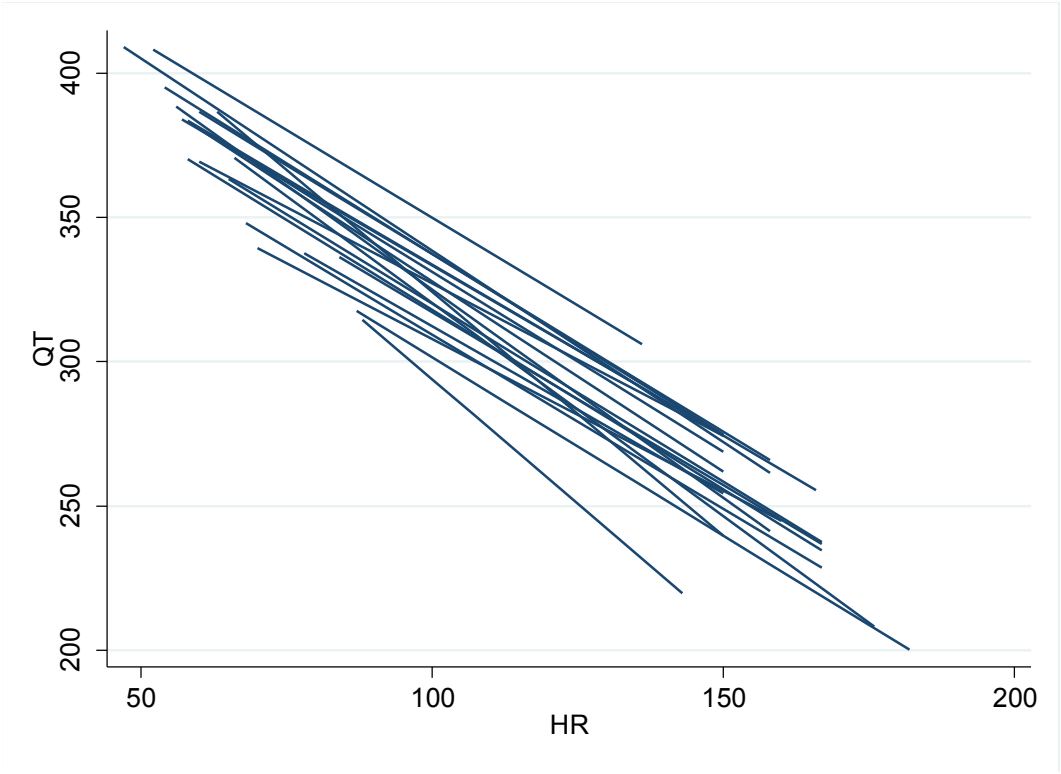

Figure 4 A

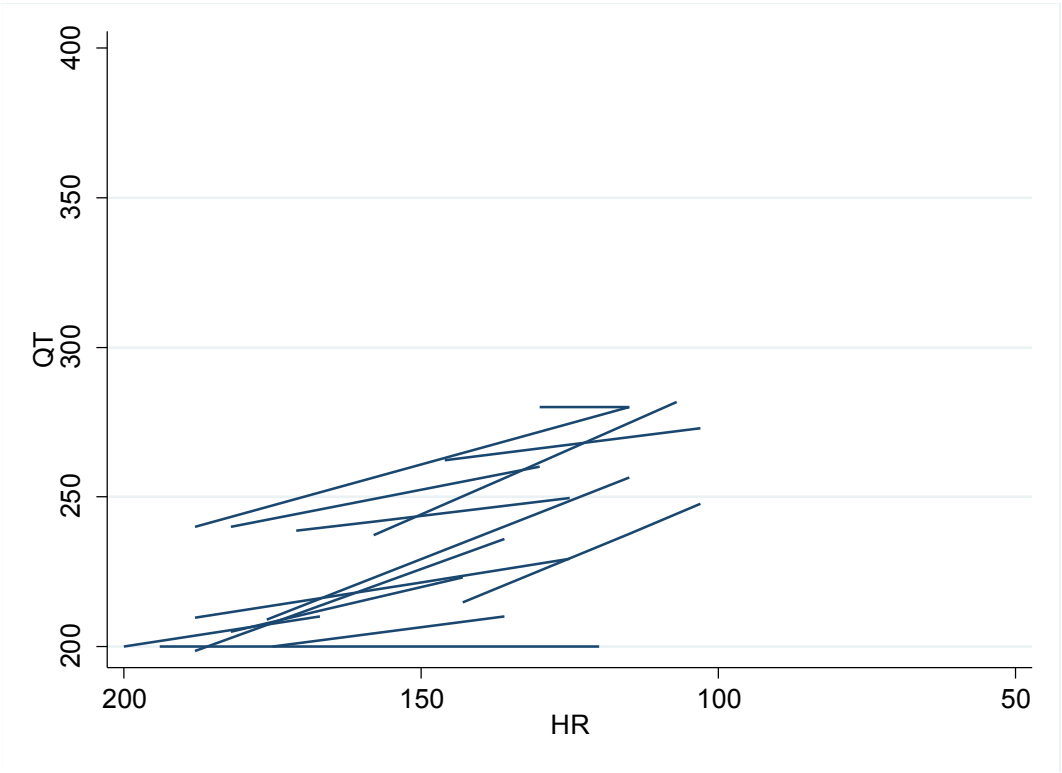

Figure 4B.