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Orthostatic Hypotension: QTc Interval Prolongation during Head-Up Tilt

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Abstract

Background: The QT interval shortens in response to sympathetic stimulation. Head-up tilt-table (HUT) testing is a straightforward way to achieve brisk sympathetic stimulation. There is not enough information about the response of the QT interval to HUT, particularly, in patients with orthostatic hypotension (OH). **Objective:** Analyse the response of the RR, QT and QTc intervals in patients with OH and reflex syncope (NM) during HUT and find differences between groups. **Methods:** We reviewed the electrocardiograms and compare the RR and QT/QTc intervals during 1) baseline; 2) HUT plus hyperventilation; 3) positive test. **Results:** We studied 137 patients, 62 control group (no syncope and negative HUT). On average, the RR HUT interval was shorter than the resting RR by −171 ± 110.4 ms in controls; −228.6 ± 119.4 ms (NM) and −194 ± (OH) ($P < 0.0001$). However, in the positive tests, the RR increased by 137.4 ± 377 ms in the NM group and in the OH group, the RR decreased by −141.1 ± 176 ms ($P = 0.002$). When the test was positive, the QTc interval shortened −27 ± 48 ms in the NM group, and in the OH group prolonged by 15 ± 32 ms ($P = 0.00001$). Furthermore, the longest QT and QTc interval values were seen in the OH group. **Conclusion:** Significant differences between the reflex group and the OH during a positive test, the QTc decreased in the NM group, but in the OH population increased. This observation has not been described. We hypothesize that QTc prolongation could reflect autonomic nervous system downregulation and could explain to a degree, the increased mortality in this group.

Keywords

Syncope, Orthostatic Hypotension, QTc Interval, Reflex Syncope, Autonomic Nervous System

1. Introduction

Syncope is a common condition characterized by a temporary loss of consciousness and postural tone. Is a symptom and often a benign condition, however, it could be a marker of underlying cardiovascular or neurological disease [1]. In patients with Parkison disease (PD) or other neurological diseases, the presence of syncope or orthostatic symptoms is associated with added mortality [2].

The QT interval is a measure of the duration of the electrical activity in the heart, which reflects the time course of ventricular depolarization and repolarization. The QT interval changes depend on the preceding RR intervals and the autonomic modulation across the ventricular myocardium. Prolonged QT interval is associated with an increased risk of arrhythmias, syncope, and sudden cardiac death [3]-[6].

The QT interval shortens in response to sympathetic stimulation and head-up tilt-table (HUT) testing is a straightforward way to achieve brisk sympathetic stimulation. *Yet, little is known about the response of the QT interval to HUT. There are reports on the QT interval changes HUT in patients with reflex syncope*. During HUT, the QT shortens less than the RR interval [7] [8]. However, there is no data about the effects of HUT on the QT interval in patients with orthostatic hypotension.

2. Objectives

Evaluate the changes in the QT and QTc intervals during HUT in patients with orthostatic hypotension and compare with subjects with reflex syncope. Our null hypothesis was to find no changes between groups.

2.1. Definitions during HUT

2.1.1. Reflex Syncope (Neurally Mediated; NM)

Reflex response mediated by the autonomic nervous system. The autonomic nervous system may overreact (increasing parasympathetic tone), leading to a sudden decrease in heart rate and blood pressure, developing syncope, positive test. The term "reflex" reflects the involvement of both the neurological and cardiovascular systems [1]-[3] [6]-[9].

2.1.2. Orthostatic Hypotension (OH)

Significant decrease in systolic blood pressure (BP) of 20 mm Hg or more or a 10 mmHg decrease in diastolic blood pressure during HUT with or without symptoms.

Patients with autonomic dysfunction or alpha-synucleinopathies (as PD) could develop OH, where cardiovascular dysautonomia is due to degeneration of postganglionic sympathetic neurons. Patients with multiple system atrophy (MSA) often present OH [1] [10] [11].

3. Methods

Between June 2017 and Jan 2024, 626 patients underwent HUT testing in two

centers: CASMU and British Hospital from Montevideo, Uruguay. HUT testing indications included dizziness, presyncope, falls and syncope. Exclusion criteria: evidence of structural heart disease, suspected LQTS, and presence of medication that could affect heart rate or QT response to HUT (e.g. beta-blockers).

Polypharmacy is defined as the regular use of five or more medications at the same time.

HUT protocol had four phases: 1) horizontal lying for 20 minutes, 2) 70 degrees HUT for five minutes, 3) at min five HUT, subjects hyperventilate for four minutes, 4) continuation of HUT until minute 21. If the patient developed symptoms (dizziness, pre-syncope, or syncope) or a significant blood pressure drop, the test was considered positive, and the patient was returned to zero degree (no inclination).

During the entire study, heart rate, blood pressure, O_2 saturation and a continuous 12-lead electrocardiographic recording were stored for further analysis.

3.1. Study Patients

From our database, we selected patients above 49 years old to generate a homogeneous group. Thus, the study included 137 patients. 62 (45%) were in the control group, all without history of syncope, negative study without abnormalities. 75 (54%) patients had a positive test; 41 were in the reflex (NM) group and 34 in the OH group as defined. Thirty-five were women in the control group (56%), 25 in the NM (60%) and eleven in the OH group (32%).

3.2. Measurements

All measurements were stored on 12-lead ECG records during HUT tests (cardiosecur.com). We measure the RR and QT intervals: 1) during rest in the supine position; 2) HUT phase during hyperventilation 3) if the patient had a positive test, the QT measurements on the previous seconds of the episode (symptoms or significant hypotension, not during long pauses). An abnormal QT or QTc interval was above 500 ms. The corrected QT (QTc) value was calculated according to the Bazzet formula.

3.3. Statistics

Data displayed as mean ± standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables. Independent sample t-test to compare HUT between groups.

To examine the hypothesis that HUT influences the QT interval and the QTc value, paired samples t-test was performed using the RR, QT, and QTc intervals as the dependent variables and the patient position ("rest" vs. "HUT" vs. "positive") as independent variable in the control, NM y OH group.

A two-tailed P-value ≤ 0.01 was significant. Fisher exact test when proper.

Regression analysis with linear curve estimation in each group and compare the different equations to create a pattern for each group.

4. Results

Table 1 shows population characteristics, where age and gender were significantly different. In the OH group, there were more males, 90%, compared to the other two groups, 43% and 39% in the control group and the NM group ($P < 0.001$).

Comorbidities were present in all groups. Arterial hypertension prevalence was present in 14 (17%), 7 (11%) and 14 (41%), control, NM, OH, respectively. Type 2 diabetes in 3 (3%) patients, 0% and 5 (14%), respectively. Only one patient from the control group had type 1 diabetes. PD or Parkinson's related diagnosis was present in one in the control group (1%), none in the NM group and in six of the OH group (17.6%). Polypharmacy on five subjects, all in the OH group, these differences were statistically significant (Table 1).

4.1. Comparison of the QT/QTc Interval between Groups

On average, the RR HUT interval was shorter than the resting RR by −171 ± 110.4 ms in controls; −228.6 ± 119.4 ms (NM) and −194 ± 150 ms (OH) ($P < 0.0001$). However, in the positive tests the RR increased by 137.4 ± 377 ms in the NM group and in the OH group the RR decreased by −141.1 ± 176 ms ($P = 0.002$).

The baseline QT was different 421 ± 30, 417 ± 20 and 432 ± 35 ms, control, NM, OH group; respectively (Figure 1).

The QT interval during HUT was shorter than resting by −28 ± 23 ms, −38 ± 25 ms and −22 ± 17 ms in controls, NM and OH groups, respectively.

When the test was positive, the QT interval was shorter than during the supine stage by −9 ± 29 ms in the NM group and −20 ± 21 ms in the OH group.

The trend in the QTc interval was different, in the NM group the QTc interval shortened −27 ± 48 ms, and in the OH group prolonged by 15 ± 32 ms ($P = 0.00001$) Figure 1 and Figure 2.

4.2. Abnormal QT/QTc Prolongation

We saw the longest QT and QTc interval values in the OH group. The QT and QTc interval values above 500 ms during baseline QT interval in one patient, baseline QTc interval in seven patients, four in the OH group. An abnormal QT interval during HUT in one patient in the OH group, QTc interval during HUT in six patients (4 in the OH group and one in each other group). During a positive test, the QT and QTc was abnormal in two and five subjects all in the OH group, respectively.

4.3. Gender Comparison

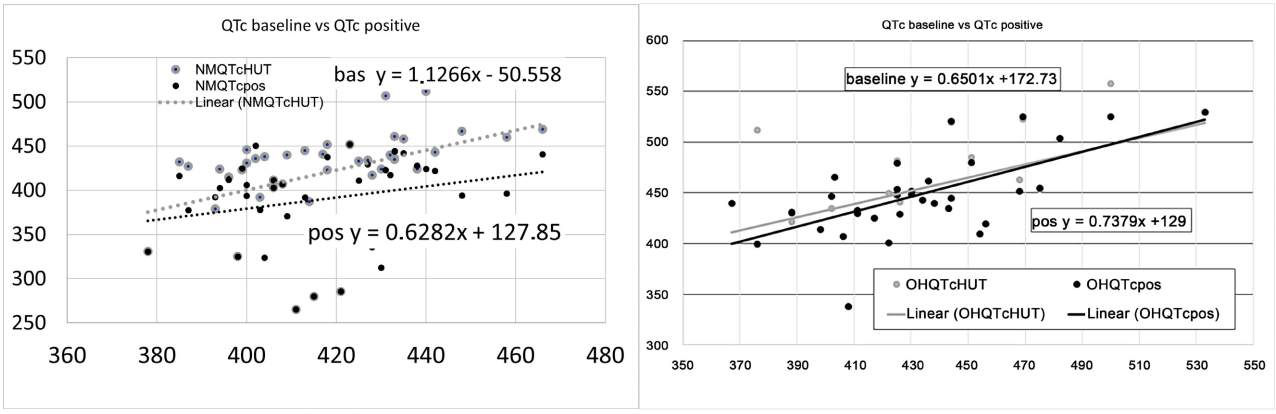
Females were predominant in the NM group 25 (60%) versus eleven (32%) in the OH group. In men, the RR interval during a positive test the QTc interval was 778 ms vs 1163 ms in the NM group, and the QTc in positive patients was 450 ms (OH) vs 372 ms in the NM group ($P = 0.01$).

Despite the female predominance in the NM group, the baseline QT was not significantly different from the OH group. In women, the two significant variables

Table 1. Population characteristics.

	Controls (negative)[a]			NM[b]			OH[c]			
	Mean ± SD	n	%	Mean ± SD	n	%	Mean ± SD	n	%	P Value
Age (years)	68 ± 11	62		62 ± 10	41		76 ± 8 ab	34		0.01 Ŧ
Female gender		35	56		25	61		32	10	0.029
HTN		14	22		7	17		14	41	0.001*
Diabetes		3	4		0	0		5	14	0.006 ŦŦ
Polypharmacy		0	0		0	0		5	14	0.0003 ŦŦ
Parkinson disease		1	1		0	0		6	17	0.00001 ŦŦ
Inclination time min	21.0 ± 2.3 bc			12.9 ± 5			11.0 ± 4.6			0.001 Ŧ
QRS ms	101± 23			96 ± 17			100 ± 18			NS
RR baseline ms	930 ± 167			937 ± 148			947 ± 154			NS
QT baseline ms	404 ± 32			402 ± 33			418 ± 40			NS
QTc baseline ms	421 ± 30			417 ± 20			432 ± 35			NS
RR HUT ms	761 ± 138			707 ± 137			774 ± 144			NS
QT HUT ms	375.2 ± 36.3			365 ± 39			394 ± 42			NS
QTc HUT ms	432.3 ± 30			437 ± 28			451 ± 41.5			NS
RR positive	NA			1073 ± 348			810 ± 188			0.01
QT positive	NA			392 ± 35			399 ± 46			NS
QTc positive	NA			389 ± 49			448 ± 41			0.01

Table 1: Patient demographics, comorbidities, and comparison between groups; NM neurally mediated or reflex syncope; OH, orthostatic hypotension. HTN, arterial hypertension; SD, standard deviation, SBP systolic blood pressure, DBP, diastolic blood pressure. MS, milliseconds, POS, positive test; NA, not applicable; *Pearson chi-square tests; ŦŦFisher exact test; *ŦResults are based on two-sided tests assuming equal variances. For each significant pair, the key to the smaller category appears in the category with the larger mean. Significance level for upper case letters (a, b, c); P = 0.01; Tests are adjusted for all pairwise comparisons within a row of each innermost subtable using the Bonferroni correction.



(a) (b)

Figure 1. We present two scattered charts a and b. with their corresponding regression lines. X axis baseline QT interval. Y axis QTc interval in positive patients. 1(a): The NM group has two parallel regression lines also with a positive correlation but widely separated during HUT and when the study is positive. 1(b): Orthostatic hypotension group, the lines are almost equivalent.

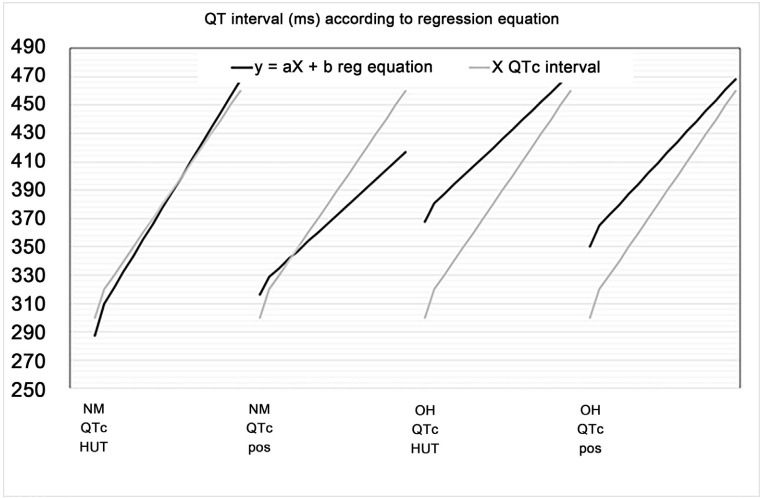


Figure 2. Each group is shown on the horizontal axis. On the vertical axis. QT interval in black from smaller to larger. And in grey, the QTc intervals generated by the regression equation obtained from the graphs in **Figure 1**. During HUT the lines follow a similar pattern. But when the test is positive. The pattern changes completely; the QTc interval in the NM group is very different, displaying a lower value. In the OH group, the lines follow almost an identical pattern. This observation suggests that NM patients are under strong regulation and the OH group, despite the marked hemodynamic variations appears under-regulated by the autonomic nervous system.

were the RR difference (RR baseline – RR positive) that was 87 ms in the OH vs -90 ms in the NM, also the average QTc interval during a positive test was 441 ms in the OH group versus 399 ms in the NM group (P = 0.01).

4.4. Comparison of the QT/QTc Intervals within Groups (Table 2 and Table 3)

4.4.1. Reflex Group (NM)

On average, the HUT RR interval was shorter than 0-degree RR interval, by 240.7 ± 139.21 ms, P < 0.0001. HUT QT interval was longer than in the supine stage by 36 ± 22 ms, P = 0.0012. HUT QTc interval value was shorter by 25 ± 27 ms, compared to the resting QTc interval (P < 0.00001). However, during syncope the QT interval was shorter by 8 ± 30 ms, P = 0.038; and the QTc interval was significantly shorter than the resting QTc interval by 29 ms ± 48 ms (P < 0.00001).

4.4.2. Orthostatic Hypotension (OH) Patients

The HUT RR interval was shorter than the supine stage RR interval by 204.1 ± 149.8 ms, P = 0.000001. HUT QT interval was shorter than supine stage by 26 ± 16 ms, P = 0.014. The HUT QTc interval value prolonged by 24.9 ± 18 ms, P < 0.001 compared to the resting QTc interval. When the test was positive, the QT interval was also shorter by 15 ± 22 ms, (P = 0.001), and the QTc interval value prolonged by 15 ± 28 ms versus the supine QTc interval (P = 0.004).

We calculated the value of the QTc interval according to the regression equation for each group (see **Figure 2**), the NM group displayed the most different

Table 2. Paired samples statistics.

		N	Mean	SD	SEM
RR Baseline	NM	41	936.8	148.3	23.2
	OH	34	946.8	164.3	28.2
QT Baseline	NM	41	401.7	33.2	5.2
	OH	34	417.6	40.2	6.9
QTc Baseline	NM	41	416.7	19.8	3.1
	OH	34	431.9	35.0	6.0
RR HUT	NM	33	706.9	137.2	23.9
	OH	28	774.0	143.6	27.1
QT HUT	NM	33	365.3	38.9	6.8
	OH	28	394.1	42.2	8.0
QTc HUT	NM	33	437.0	28.1	4.9
	OH	28	451.0	41.5	7.8
RR pos	NM	40	1073.0	347.7	55.0
	OH	33	809.5	188.2	32.8
QT pos	NM	40	392.1	35.0	5.5
	OH	33	398.8	46.4	8.1
QTc pos	NM	40	389.2	49.5	7.8
	OH	33	447.5	41.0	7.1

SD, standard deviation, HUT head-up-tilt, SEM standard error mean, POS, positive test.

Table 3. Independent paired samples test.

	Mean Difference	Std. Error Difference	95% CI	95% CI	Sig. (2-tailed)
			Lower	Upper	
RR Baseline	−15.9	8.6	−33.1	1.3	0.070
QT Baseline	−15.2	6.8	−28.8	−1.7	0.029
QTc Baseline	−10.0	36.5	−82.8	62.8	0.785
RR HUT	−67.1	36.2	−139.5	5.4	0.069
QT HUT	−28.8	10.5	−49.8	−7.8	0.008*
QTc HUT	−13.9	9.2	−32.5	4.7	0.138
RR pos	263.5	64.0	135.6	391.4	0.00011*
QT pos	−6.7	9.8	−26.3	12.9	0.499
QTc pos	−58.3	10.6	−79.5	−37.2	0.000000*

HUT head-up-tilt, CI. confidence interval, POS, positive test.

graph. In the OH group, the calculated QTc curve is the same than the OH QT HUT line.

The comparison of the QTc intervals is shown in Figure 3, where we can see a significant difference with a much longer QTc intervals in the OH group (Figure 3).

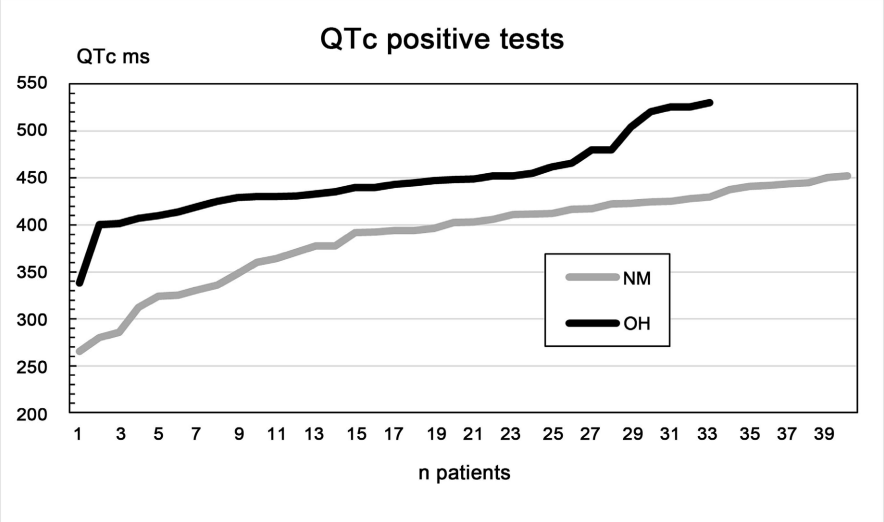


Figure 3. Linear graph showing the differences between the QTc interval in positive patients. As shown the QTc interval in the OH group is much longer than the NM group.

t-Test: Two-Sample Assuming Unequal Variances.

		QTc OH	QT NM
Mean		453.38	379.36
Variance		1714.44	2486.40
Hypothesized Mean Difference	0		
df		42	
t Stat		6.69	
P (T ≤ t) two-tail		0.0000001	
t Critical two-tail		2.69	

5. Discussion

During HUT there is a reduction on the venous return; the autonomic nervous system compensates by altering the autonomic tone, resulting in an increase in heart rate and constriction of blood vessels in the legs. Changes include an increase of sympathetic tone, withdrawal of parasympathetic tone and variations in circulatory catecholamines. These variations may affect the QT interval independently of the changes in heart rate [3]-[8] [12]-[22]. QT variations are not simultaneous, a delay of the QT response was seen during exercise [23]-[26]. The QT interval shortens in response to exercise and atropine, and vagal inhibition with or without concomitant sympathetic excitation [5] [24]-[30].

According to earlier studies, the QT interval had no significant variations during reflex syncope [7]. In reflex syncope, the sympathovagal balance changes, leading to sympathetic predominance just before sudden vagal discharge [31]-[33]. Changes in QT intervals during reflex syncope could reflect autonomic modulation of ventricular repolarization [8]-[34]. Jaeger *et al.* reported that QT intervals remained short in the presence of profound bradycardia during reflex cardioinhibitory syncope [8]. Our study is consistent with these findings.

5.1. Two Mechanisms Are Plausible

First, residual cardiac sympathetic stimulation on ventricular myocardium despite

marked vagal influence on the sinus node and withdrawal of sympathetic effect on peripheral vasculature may contribute to failure of QT prolongation during the bradycardia induced by the reflex syncope [8] [35].

Second, paradoxical shortening of QT interval after a prolonged pause was reported in patients with bradycardia due to sick sinus syndrome or atrioventricular block [34] [35]. This paradoxical response may indicate an unusual adaptation of repolarization time to abrupt increase in the preceding R-R interval not mediated by the autonomic nervous system [36]. Castellanos et al. reported that the QT interval at the end of vagal-induced R-R pauses initially showed no prolongation as the pauses lengthened to 2450 ms [34].

The QT interval changes could reflect the autonomic modulation occurring during NM syncope and serve as an "autonomic barometer" [8].

Changes in autonomic tone may condition the QT interval both indirectly, by modulating heart rate and directly by affecting depolarization and repolarization kinetics of myocardial cells through neural and receptor-mediated mechanisms [37].

In our study and an earlier one from our group, we found significant differences between the reflex group with the OH patients, the QTc decreased in the NM group and increased in the OH subjects [38].

We hypothesize that the QTc prolongation reflects the absence of autonomic regulation, suggesting an inadequate response of the autonomic nervous system despite the presence of severe arterial hypotension.

5.2. Orthostatic Hypotension Mechanism

Normally, unloading of the baroreceptors by standing up initiates norepinephrine release from sympathetic post-ganglionic nerves causing vasoconstriction, which keeps BP in the standing position. This compensatory vasoconstriction is absent or attenuated in patients with synucleinopathies, resulting in neurogenic OH (nOH).

The site of the "autonomic lesion" in the baroreflex pathways responsible for cardiovascular autonomic dysfunction is different in patients with Lewis Body (LB) disorders versus MSA. In patients with LB disorders, cardiovascular dysautonomia is due to degeneration of post-ganglionic sympathetic neurons [39]. A meta-analysis of thirteen prospective studies, including 121,913 individuals found that OH increased all-cause mortality at 5-year follow-up by 1.5 times [40]. Other studies found the OH population had a 2.5-fold increased risk of mortality compared to those without OH [41] [42].

In our study, we found QT prolongation in OH patients that may lead to sudden cardiac death in this population.

6. Limitations

We designed an observational study using a comprehensive database to assess changes in QT, RR, and QTc relations, and evaluate the QTc differences between the patients with OH and other conditions.

Subgroups are small.

We did not perform any blood analysis or other measurements to evaluate autonomic nervous system activity during the test.

We did not analyze our results using the Fridericia and Framingham formulas.

7. Conclusion

We saw significant differences between the reflex group and the OH patients when the test was positive, the QTc decreased in the NM group. In the OH population, it has increased in most patients. This observation has not been described. We hypothesize that the QTc prolongation could reflect autonomic nervous system downregulation and could explain in part, the increased mortality in this population.

Statement of Human and Animal Rights

The study was by the ethical standards of the Declaration of Helsinki and its later amendments.

Conflicts of Interest

There are no conflicts of interest to declare.

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