

Early Screening of Hypertension and Cardiac Dysautonomia in Each Hypertensive is Needed-inference from a Study of QTc Interval in Gujarat, India

Abstract

Background: Hypertension (HTN) is linked to cardiac dysautonomia that can end up as life-threatening arrhythmias. The same can be screened by simple electrocardiogram (ECG)-based QTc (QT corrected for heart rate) interval which indicates repolarization abnormality. We quantified QTc interval among treated hypertensives in comparison to controls, testing effect of age, gender, and blood pressure. **Methods:** We conducted a cross-sectional study was done at a tertiary care teaching hospital of Gujarat, India, on 142 hypertensives on monotherapy (60 males, 82 females) and 72 age-, sex-, and time-matched normotensives. ECG was recorded with minimum 10 complexes of Lead II. QTc was derived from average of 10 values, using Bazett's formula. QTc > 0.43 s in male and > 0.45 s in female was considered abnormal. **Results:** Hypertensives (mean age 40 and duration 5 years) had significantly higher QTc value than normotensives among males (0.42 vs. 0.40, $P < 0.001$), females (0.44 vs. 0.41, $P < 0.001$), and in total (0.43 vs. 0.41, $P < 0.001$) with 24% prevalence of ECG-based left ventricular hypertrophy. Hypertensives had odds ratio 1.63 in males ($P = 0.15$), 23.71 in females ($P = 0.003$), and 3.83 in total ($P < 0.001$) for prolonged QTc. QTc values were significantly affected by increasing age amongst hypertensives but not by duration of HTN or current blood pressure. **Conclusions:** Our study showed a high prevalence of prolonged QTc, both qualitatively and quantitatively, in hypertensives on monotherapy with poor pressure control, associated with female gender and age but not duration or blood pressure. This underscores high risk of repolarization abnormality induced future event, suggesting QTc screening as primary prevention.

Keywords: Blood pressure, gender, hypertensive, QTc interval, repolarization

Introduction

Hypertension (HTN), being prevalent in one out of three urban Indian,^[1] is responsible for 10% of all deaths^[2] and projected to double in number from 2000 to 2025. With majority being undiagnosed, affected comparatively at young age,^[2] and just one-fifth having blood pressure controlled,^[1] it imposes risk of left ventricular hypertrophy (LVH). This can produce repolarization abnormalities^[3] and can cause life-threatening arrhythmia^[4] which if unchecked, end up as sudden cardiac death.^[5] Repolarization abnormality can be diagnosed by a simple, objective, validated tool QTc interval^[6] derived from simple electrocardiogram (ECG), using Bazett's formula.^[7] Prolonged QTc is a known risk factor to cause cardiovascular morbidity and mortality,^[5,6] especially in the presence of cardiovascular diseases (CVDs).^[8] Despite

this, we could not find any study relating QTc interval in HTN from our region. QTc in HTN is affected by multiple factors: Age, gender, and pressure control being three of them, which we tried to study in our population along with the prevalence of QTc prolongation by a horizontal study.

Methods

Study type

We conducted a cross-sectional case study in association with Physiology Department of our college.

Permission

Prior permission of Physiology Department was followed by approval of institutional review board of our college. Written consent from participants undergoing study was taken who were also informed about aim of this study.

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Sample size

Sample size was calculated by software RaoSoft (RaoSoft, Inc., free online software, Seattle, WA, USA) for population of the city 6 lakhs with 35.8% prevalence of HTN in west India.^[1] A size of 142 (82 males, 60 females) was sufficient to yield 90% confidence level keeping 10% margin of error.

Study subject-case

We recruited 142 under treatment hypertensive patients (newly diagnosed and known) from general outdoor patient departments of a teaching tertiary care hospital attached to our government medical college. Patients underwent an initial assessment containing personal details, disease history, drug history, medical history, and measurement of blood pressure by sphygmomanometer.

Inclusion and exclusion criteria-case

We included hypertensives taking regular treatment as outdoor patients, ready to give written informed consent, aged between 20 and 50 years of either sex. We excluded participants aged more than 50 years, having any complication, taking irregular treatment, taking drugs that prolong QTc interval,^[9] taking drugs affecting autonomic nervous system, having cardiovascular disorders, renal failure, cancer, AIDS, tuberculosis, cardiac arrhythmia, having pacemaker, or not ready to give informed consent.

Inclusion and exclusion criteria-controls

To compare with cases, we enrolled 72 time-matched normotensive participants attending same outdoor patient departments for physical fitness or other minor ailments, ready to give written informed consent, aged between 20 and 50 years of either sex, not having cardiovascular disorders, renal failure, cancer, AIDS, tuberculosis, cardiac arrhythmia, pacemaker, and not taking any drug that affects QTc interval.^[10]

QTc measurement^[11]

We used 12 channel ECG machine to record strip ECG with standard norms. Participants were asked to lie in supine position, and ECG Lead II with minimum 10 waveform complexes was recorded on ECG machine. QT interval and RR interval were measured manually from the ECG strip for 10 successive readings. QT interval was measured using tangent method. RR interval was measured from one R-wave peak to another R-wave peak. QTc intervals were derived using Bazett's formula, and average of 10 results was taken for each participant. Seven cases and four controls were discarded since Lead II had artifact or shallow T-wave as well as difficult measurement of the QT.

Bazett's formula:

$$QTc = \frac{QT}{\sqrt{RR}}$$

No correction was used if heart rate was <60.

Electrocardiogram left ventricular hypertrophy criteria

We used the Cornell voltage criteria to define LVH which is as follows:^[11]

- S in V3+ R in aVL >28 mm (men)
- S in V3+ R in aVL >20 mm (women).

Defining norms

QTc interval value >0.43 s in male and >0.45 s in female was considered as abnormal.^[12]

Blood pressure - systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg - was defined as controlled blood pressure.

Statistical analysis

All data were processed by Microsoft Excel spreadsheet; descriptive analysis was expressed as mean \pm standard deviation and categorical data as number (percentage). All calculations were done by GraphPad InStat 3 software (demo version free software of GraphPad Software, Inc. California, USA). Observed difference in mean distribution of QTc intervals was compared by Student's *t*-test. We evaluated strength of association between QTc and various parameters by calculating odds ratio, keeping confidence interval 95%, taking QTc >0.43 s in males and QTc >0.45 s in females as positive outcomes, and QTc \leq 0.43 s in males and QTc \leq 0.45 s in females as negative outcome. Categorical data were tested for significant difference in distribution between groups by Fisher's exact test. Any observed difference was considered significant statistically with $P < 0.05$.

Results

As shown in Table 1, case group for the present study ($n = 142$) had mean age 40.7 years, representation of both sexes, mean duration of HTN 5 years, with mean values of both SBP and DBP on higher side. Majority of cases were treated by monotherapy in the form of angiotensin converting enzyme (ACE) inhibitors or calcium channel blockers (CCBs). Twenty-nine hypertensives (20%) had coexisting diabetes mellitus while hyperlipidemia (5%) and cardiac disease (4%) prevailed in minority. Smoking (37%) and drinking (22%) were moderately prevalent, and nearly half cases (47%) had positive family history of HTN.

Hypertensive Cases had significantly higher values of QTc interval in comparison to normotensive controls in total (0.43 s vs. 0.41 s, $P < 0.001$) as well as among groups based on gender (males - 0.42 s vs. 0.40 s, $P < 0.001$, females - 0.44 s vs. 0.41 s, $P < 0.001$). Hypertensive females had significantly higher QTc than hypertensive males (0.44 s vs. 0.42 s, $P = 0.006$), but normotensive females were not significantly different from normotensive males for the same (0.42 s vs. 0.41 s, $P = 0.70$) [Table 2]. We compared LVH using ECG-based Cornell voltage criteria between group, and it revealed that cases had

Table 1: Baseline data of study groups-case and control

Parameter	Value (%)
Age in years (mean±SD)	
Case (n=142)	40.70±6.80
Control (n=72)	38.28±8.27
Number of participants	
Male – case	82 (58)
Female – case	60 (42)
Total – case	142 (100)
Male – control	39 (54)
Female – control	33 (46)
Total – control	72 (100)
Duration of hypertension in years - case (mean±SD)	5.31±4.86
SBP - case (mean±SD)	142.96±18.55
<140 mmHg	24 (17)
DBP - case (mean±SD)	94.90±15.22
<90 mmHg	42 (30)
Treatment modality-case (n)	
ACEI users	90 (63)
CCB users	58 (41)
Risk factor prevalence-case (n)	
Diabetes mellitus	29 (20)
Hyperlipidemia	7 (5)
Smoking	53 (37)
Alcoholism	31 (22)
Cardiac disease	6 (4)
Positive family history	67 (47)
Neurotoxic drug exposure	0

SBP=Systolic blood pressure, DBP=Diastolic blood pressure, SD=Standard deviation, ACEI=Angiotensin converting enzyme inhibitor, CCB=Calcium channel blocker

Table 2: Quantitative comparison (mean) of QTc values (s) between hypertensives and normotensives

Group	Mean±SD		P
	Case-QTc value	Control-QTc value	
Male [†]	0.42±0.03 (n=82)	0.40±0.03 (n=39)	<0.001*
Female [†]	0.44±0.03 (n=60)	0.41±0.03 (n=33)	<0.001*
Total	0.43±0.04 (n=142)	0.40±0.03 (n=72)	<0.001*

*Statistical significance, [†]For differences of male versus female QTc value in case group. SD=Standard deviation

significantly higher values of these criteria. ECG-based LVH was more prevalent in case group than control group (24% vs. 6%, $P = 0.001$) [Table 3].

We did qualitative comparison of QTc interval among cases and controls based on standard cutoff points of normalcy. It showed odds ratio for prolonged QTc interval to be 1.6 for male hypertensives ($P = 0.15$), 23.71 for female hypertensives ($P = 0.003$), and 3.83 for all hypertensives ($P < 0.001$) as compared to normotensives, with statistical significance for all associations except for male gender [Table 4].

We performed quantitative comparison of QTc values in hypertensives by subgrouping based on age, duration,

and blood pressure control [Table 5]. Hypertensives with age >40 years, duration of HTN ≥ 5 years, SBP ≥ 140 mmHg, and DBP (SBP) ≥ 90 mmHg, did not significantly differ in QTc value than those with age ≤ 40 years, duration of HTN <5 years, SBP <140 mmHg, DBP (SBP) <90 mmHg, respectively. Quantitative QTc [left half of Table 5] did not reveal true picture which was disclosed by qualitative comparison of QTc values [right half of Table 5]. Qualitative QTc prolongation was done among hypertensive subgroups based on standard cutoff points of normalcy for age, duration, and blood pressure control [Table 5]. Hypertensives with age >40 years showed significantly higher prevalence of QTc interval as compared those with age ≤ 40 years (49% vs. 31%, $P = 0.03$). Hypertensives with duration of HTN ≥ 5 years had higher prevalence of abnormally prolonged QTc value than those with duration of HTN <5 years (45% vs. 36%, $P = 0.16$), but it lacked statistical significance. The prevalence of QTc prolongation was almost comparable between subgroups based current control of SBP (41% vs. 42%, $P > 0.99$) or DBP (40% vs. 43%, $P = 0.85$).

Discussion

HTN is ranked second to child underweight for age, attributable for deaths, and disease burden in South Asia.^[13] In India, HTN is a significant public health issue for cardiovascular health. HTN is prevalent in 33% of urban India, and majority are undiagnosed or undertreated,^[11] and this is the prime time to effectively address this health issue.^[14] HTN, despite antihypertensive treatment, can lead to LVH, which along with uncorrected cardiac dysautonomia makes cardiac repolarization abnormally prolonged.^[15] This repolarization abnormality remains silent and may progress to atrial^[16] and ventricular^[4] arrhythmias. It can lead to torsades de pointes threatening ending up as sudden cardiac death,^[17] which is seen in nearly half of the cardiac deaths in India.^[18] QTc interval measured by simple ECG is a parameter that can quantify the repolarization abnormality in hypertensives. As previously published, manually measured QT intervals correlated well with machine coded ones, and the method of QT correction for heart rate did not significantly affect the observed associations.^[5] Prolonged QTc is an established risk factor for all-cause morbidity and mortality in not only hypertensive patients^[6] but also in general population.^[19] QTc is studied extensively in western world and used as a part for risk assessment in multiple conditions including diabetes and HTN.^[8] Despite all these, it is underused and underrated in India.

We found age- and sex-matched under treatment hypertensives to have significantly higher QTc values than normotensives. The prevalence of abnormally prolonged QTc among hypertensive was 41% that is higher than other studies - 12.5% by Johnson *et al.*^[20] and 28.3% by Karaye.^[21] This can be attributed to poor blood pressure

control among the participants which is the feature of Indian hypertensives.^[1] In an unpublished part of this study, we highlighted three other results. (1) We have found effect of coexisting risk factors such as diabetes, smoking, alcoholism, and positive family history of HTN as additive, in line with known literature, especially diabetes.^[22] (2) Newly diagnosed (duration <6 months) hypertensives (26 out of 142) had a high prevalence of QTc prolongation, which may contribute to overall high prevalence. (3) There is not much significant effect of type of antihypertensive monotherapy used in hypertensives who were not on diuretics and beta-blocker. This rejects hypothesis that antihypertensive therapy can significantly modify QT interval duration by class difference,^[23] especially when we compare CCB and ACE inhibitors used as monotherapy. Prolonged QTc interval is seen in 10% of normal females and 5% of normal males,^[24] but it becomes significant in the presence of CVD risk factors such as HTN.^[8] It is proven that QTc prolongation is earlier than LVH in

untreated hypertensives^[25] and same abnormality can be seen even without LVH.^[21] We found QTc to be raised with advancing age in hypertensives with age group 20–50 years with mean age 40 years. Most previous studies have given the same correlation between QTc and age, but in older participants,^[6] our finding proves the same in relatively younger hypertensives. Mean duration of HTN was 5 years which is adequate to give a chance of structural remodeling,^[26] but LVH progresses despite antihypertensive treatment as previously documented, more so if blood pressure is not controlled like our study group. We found hypertensives in total and hypertensive females to have more prolonged QTc than normotensives ones, but same being insignificant for male gender. Similarly, males had better QTc interval than females in hypertensive group. This gender bias is in line with previous studies^[9,24,27] and can be explained by gender differences in cellular electrophysiology and autonomic modulation.^[27] Gender difference for QTc remains up to the age of 50 years^[27] and same is proven in our study and can explain odds ratio of 23.1 for QTc prolongation in female hypertensive than female normotensives.

We did not find correlation between blood pressure and QTc values that is unlike most other studies.^[28] As only 17% hypertensive subjects had diastolic and only 30% had SBP controlled, we cannot find the true picture. There was also higher prevalence of LVH based on ECG voltage criteria in hypertensives compared to control (24% vs. 6%), in line with studies done elsewhere^[29] that indicates delay in diagnosis and onset of antihypertensive treatment. LVH is additive for cardiac repolarization abnormality, and this simple variable can be calculated from same ECG along with QTc interval and other parameters of interest for

Table 3: Comparison of electrocardiogram left ventricular hypertrophy (Cornell voltage criteria) between case and control group

Parameter	Case group (n=142)	Control group (n=72)	P
RaVL (mm), mean±SD	10.3±4.58	5.2±1.91	<0.001*
SV3 (mm), mean±SD	12.5±4.02	7.1±2.24	<0.001*
ECG LVH, n (%)			
Present	34 (24)	4 (6)	0.001*
Absent	108 (76)	68 (94)	

*Statistical significance. RaVL=R-wave amplitude in lead aVL, SV3=S-wave amplitude in lead V3, LVH=Left ventricular hypertrophy, ECG=Electrocardiogram, SD=Standard deviation

Table 4: Qualitative comparison of QTc values (normal or abnormal) between hypertensives and normotensives

	QTc value of cases		QTc value of controls		OR	95% CI	P
	Abnormal, n (%)	Normal, n (%)	Abnormal, n (%)	Normal, n (%)			
Male	32 (39)	50 (61)	10 (26)	29 (74)	1.86	0.780,4.31	0.15
Female	26 (43)	34 (57)	1 (3)	31 (97)	23.71	3.03,185.2	0.003*
Total	58 (41)	84 (59)	11 (15)	62 (85)	3.83	1.85,7.89	<0.001*

*Statistical significance. OR=Odds ratio, CI=Confidence interval

Table 5: Quantitative (mean in s) and qualitative (normal or abnormal in number) comparison of QTc values among hypertensives by grouping based on age, duration, and blood pressure control

Parameter	Cutoffs	n (%)	QTc (mean±SD)	P	QTc-AbN, n (%)	QTc-N, n (%)	P
Age (years)	≤40	65 (46)	0.43±0.04	0.80	20 (31)	43 (69)	0.03*
	>40	77 (54)	0.43±0.03		38 (49)	41 (51)	
Duration (years)	<5	67 (47)	0.43±0.04	0.90	24 (36)	43 (64)	0.16
	≥5	75 (53)	0.43±0.03		34 (45)	41 (55)	
Systolic pressure (mmHg)	<140	24 (17)	0.44±0.05	0.43	10 (42)	14 (58)	>0.99
	≥140	118 (83)	0.43±0.03		48 (41)	70 (59)	
Diastolic pressure (mmHg)	<90	42 (30)	0.44±0.04	0.18	18 (43)	24 (57)	0.85
	≥90	100 (70)	0.43±0.03		40 (40)	60 (60)	

*Statistical significance. QTc-N=Normal QTc value, QTc-AbN=Abnormally prolonged QTc value, SD=Standard deviation

prognosis.^[30] Short-term beat-to-beat variability of QTc interval is a novel marker that correlates with LVH,^[31] but we did not find it. Prolongation of QTc is seen even if blood pressure is under control^[32] and in the absence of LVH in HTN, making QTc interval an independent CVD risk factor. According to one meta-analysis, QTc interval with antihypertensive therapy was not associated with therapeutic blood pressure response. Although elevated, unchecked blood pressure despite ongoing treatment makes participant vulnerable to LVH. Mere blood pressure measurement cannot give inference about underlying repolarization abnormality and potential of arrhythmia.

HTN is an iceberg disease and a serious health-related issue affecting individuals in reproductive age group.^[14] Despite blood pressure lowering, there is a significant residual cardiovascular risk attributable in part to greater subclinical disease burden. Hypertensives are under a possible threat of repolarization abnormalities owing to build up of heterogeneous mass imposing risk of varying degree of arrhythmia.^[33] Hence, screening of undiagnosed hypertensive by simple blood pressure measurement on large scale and measuring at risk hypertensive by simple ECG deriving QTc can serve as a good primary prevention. Drugs such as CCBs and ACE inhibitors are proven to be protective against the hypertrophy by inducing favorable cardiac structural remodeling,^[34] but same is not true for repolarization abnormality.^[35] None of the patients of our case group was offered β -blocker, which is preventive for arrhythmia.^[17] A recent study^[36] performed on outpatient cases with end-stage renal disease, and HTN indicates that the higher prevalence of prolonged QTc interval is not related to the three established factors such as age, SBP, and DBP. Thus, it appears that prolonged QTc is a complex phenomenon, which may be unaffected by these risk factors. This could be due to the consequences of different vectors and factors that can affect myocyte repolarization quality, which should be monitored in risk groups as a main criterion that increase mortality rate. The American Heart Association and American College of Cardiology Foundation have recommended ECG as a simple noninvasive diagnostic test to stratify CVD risk in patients with HTN and diabetes.^[37] QTc, such as measurement of blood pressure, does not require any specialized technique, and this cost-effective method can be used by even general practitioners or family physicians to whom majority of hypertensives consult. Adding QTc value as an objective tool strengthens, CVD risk stratification and early screening of at-risk hypertensives with prompt treatment can prevent abnormal aftermaths, if used optimally.

Limitations of study

The study was limited by small sample size, manual measurement of QTc interval, and presence of confounding factors which cannot be negated. Due to cross-sectional nature, it fails to establish causality with certainty but

definitely warrants further work in this direction and optimum use of a tool such as QTc interval.

Conclusions

In Gujarati hypertensives on monotherapy with poor pressure control, we found higher values of QTc interval as compared to normotensives, with female disadvantage. HTN seemed to impose significant prevalent risk of prolonged QTc which correlated with age but not with duration and current blood pressure value. Early screening of HTN, prompt treatment, measurement of QTc to identify at-risk hypertensives and appropriate intervention with strict blood pressure control can be included as a primary preventive strategy.

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Conflicts of interest

There are no conflicts of interest.

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