Research Paper

QTc interval in young Gujarati hypertensives: Effect of disease, antihypertensive monotherapy, and coexisting risk factors

Jayesh Dalpatbhai Solanki, Bhakti P. Gadhavi, Amit H. Makwana, Hemant B. Mehta, Chinmay J. Shah, Pradnya A. Gokhale

Department of Physiology, Government Medical College, Bhavnagar, Gujarat, India

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ABSTRACT

Objectives: To study the effect of disease duration, treatment and risk factors on QTc interval among young hypertensives. **Materials and Methods:** A case–control study was conducted on 142 hypertensives (60 males, 82 females) taking calcium channel blocker (CCB) or angiotensin-converting enzyme inhibitor (ACEI) as monotherapy. After blood pressure measurement, we recorded lead II electrocardiograph with minimum ten waveforms. QTc was derived from average of ten values using Bazett's formula. QTc interval >0.43 s in male and >0.45 s in female was considered abnormal. **Results:** Cases had mean duration of hypertension 5 years, mean age of 40 years, and poor blood pressure control (systolic blood pressure >140 and diastolic blood pressure >90 mm of Hg). Newly diagnosed hypertensives had significantly higher QTc values than the matched known cases (0.44 vs. 0.42 s, $P < 0.05$). Known hypertensives did not differ significantly in QTc values by the duration of disease. CCB users showed small, insignificant disadvantage for abnormally prolonged QTc values than ACEI users. With coexisting diabetes, smoking, and positive family history of hypertension, there was odds risk of 7.69, 2.75, and 2.54, respectively for prolonged QTc. **Conclusion:** Our study showed prolonged QTc in hypertensives more so in newly diagnosed, unaffected by duration or use of ACEI, or CCB but associated with modifiable risk factors. This underscores high risk of repolarization abnormality-induced future events, suggesting early screening of hypertension, strict blood pressure control, optimum use of QTc measurement, and preventive pharmacotherapy to reduce this aftermath.

Key words: Antihypertensive, arrhythmia, duration, hypertension, QTc interval

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Address for correspondence:
Jayesh Dalpatbhai Solanki, F1, Shivganga Appartments, Plot No 164, Bhayani Ni Waadi, Opp. Bawaliya Hanuman Temple, Gadhechi Wadlaa Road, Bhavnagar - 364 001, Gujarat, India.
E-mail: drjaymin_83@yahoo.com

INTRODUCTION

There is an alarming rise of hypertension in India,[1] and one of the three individuals has a risk of hypertension, which calls

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for a felt need to effectively fight against it. Involvement at young age, the majority of undiagnosed patients, poor pressure control, irregular treatment, and reduced awareness about hypertension further complicate the risk profile picture.[2] Left ventricular hypertrophy (LVH) and cardiac dysautonomia can lead to repolarization abnormality,[3] which if unaddressed can progress to life-threatening arrhythmia,[4] resulting in sudden cardiac death. However, it can be diagnosed by QTc (QT corrected for heart rate) interval measured by simple electrocardiograph (ECG) using Bazett's formula.[5] Life-threatening arrhythmia can also be prevented using drugs such as angiotensin-converting enzyme inhibitor (ACEI), calcium channel blocker (CCB), and β-blockers, the last of which is having proven efficacy[6] but not used as monotherapy routinely. With increased duration of hypertension and in the presence of various risk factors,[7,8] such as smoking, diabetes, alcoholism and positive family history of hypertension, QTc abnormality is bound to worsen. On the contrary, ACEI and CCB that benefit by cardiac structural remodeling[9] are not proven to affect QTc. We studied the effect of duration, antihypertensive treatment, and associated-risk factors on QTc interval in hypertensives as perhaps the first such study from Gujarat region.

MATERIALS AND METHODS

Study type

We conducted a case–control study in association with Physiology Department of our college.

Permission

Prior permission of Physiology Department was followed by approval of the Institutional Review Board of Government Medical College, Bhavnagar, Gujarat, India. Written consent from patients undergoing study was taken who were also informed about the aim of this study.

Sample size

The 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 hypertension 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 subjects

We recruited 142 under treatment hypertensive patients (newly diagnosed and known) from general outdoor patient departments of a teaching tertiary care hospital attached to Government Medical College, Bhavnagar. 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

We included hypertensives taking regular treatment as out-patients, ready to give written informed consent, aged between 20 and 50 years of either sex. We excluded patients having complications of hypertension, taking irregular treatment, taking drugs that prolongs QTc interval,[10] 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.

QTc measurement[11]

We used 12 channel ECG machine to record strip ECG with standard norms. Patients were asked to lie in the supine position, and ECG lead II with minimum ten waveform complexes was recorded on ECG machine. QT interval and RR interval were measured manually from the ECG strip for ten successive readings. QT interval was measured by tangent method.[11] 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 ten results was taken for each subject. Seven cases were discarded since lead II had artifact, shallow T wave, or difficult measurement of the QT.

Bazett's formula:

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

No correction was used, if heart rate was <60.

Defining norms

QTc interval - value >0.43 s in male and >0.45 s in female, was considered as abnormally prolonged.[12]

Blood pressure - systolic blood pressure (SBP) <140 mm of Hg and diastolic blood pressure (DBP) <90 mm of Hg, was defined as controlled blood pressure.[13]

Statistical analysis

The data were transferred on Excel spreadsheet. Quantitative data were expressed as mean ± standard deviation, and qualitative data were expressed as number. All calculations were done using Graph Pad In Stat 3 software (demo version free software of GraphPad Software, Inc. California, USA). Observed difference in the mean distribution of QTc intervals was compared by Student's unpaired *t*-test. We evaluated the strength of association between QTc and various parameters by calculating odds risk, keeping confidence interval 95%. For qualitative comparison, QTc >0.43 s in males and QTc >0.45 s in females was considered as positive outcomes and QTc ≤0.43 s in males and QTc ≤0.45 s in females was considered as negative outcome. Categorical data were evaluated for

comparison by Fisher's exact test. Any observed difference was considered statistically significant with $P < 0.05$.

RESULTS

As shown in Table 1, case group of the present study ($n = 142$) had mean age of 40.7 years, representation of both sexes, and mean duration of hypertension 5 years. Twenty-six were newly diagnosed cases (duration <6 months), mean values of both SBP (143 mm of Hg) and DBP (95 mm of Hg) were higher than recommended,[13] and majority were treated by monotherapy in the form of ACEI or CCBs. Twenty-nine hypertensives had coexisting diabetes mellitus while hyperlipidemia (7/142) and cardiac disease (6/142) prevailed in the minority. Smoking (53/142) and alcoholism (31/142) were highly prevalent, and nearly half cases had positive family history of hypertension.

Comparison of QTc values between newly diagnosed hypertensives (duration <6 months) and known hypertensives matched by age and gender (13 males and 13 females, 26 in total in each group) showed that new cases had higher QTc values than known cases, with statistical significance. Similarly, newly diagnosed hypertensives had statistically higher prevalence of prolonged QTc interval as compared to matched known cases [Table 2].

We did comparison of QTc values between known hypertensives (duration >1 year) among groups based on duration of disease, matched by age and gender (26 males and 13 females, 39 in total in each group). It showed that hypertensives with duration more than 5 years had slightly longer QTc interval values as well as slightly higher prevalence of prolonged QTc interval than hypertensives with duration <5 years, but it was statistically insignificant [Table 3].

Comparison of QTc values between CCB user hypertensives and age, gender, disease duration matched ACEI user hypertensives (29 males and 22 females, 51 in total in each group), showed ACEI users to have higher QTc values than CCB users, but the prevalence of prolonged QTc interval was slightly more in CCB users than ACEI users in newly diagnosed cases, in hypertensives treated for <5 years and in total. However, these results lacked statistical significance [Table 4].

There was a negative correlation between SBP, DBP, and mean blood pressure with QTc values that was insignificant statistically [Table 5].

We studied the effect of the presence of individual coexisting risk factor on QTc values between matched subgroups of hypertensives, based on the presence or absence of risk factor, in terms of values as well as the prevalence of abnormal QTc interval. Hypertensives with either diabetes ($n = 29$), smoking ($n = 53$), and positive family history ($n = 67$) had significantly higher QTc values, both qualitatively and quantitatively than matched hypertensives without it, imposing significant odds risk of prolonged QTc values 7.69, 2.75, and 2.54, respectively. However, the presence of alcoholism did not significantly affect QTc values as compared to those without it [Table 6].

Table 1: Baseline data of hypertensive cases of the study group

Parameter	Value
Age (years), mean±2SD	40.70±13.60
Number of patients	
Male	82
Female	60
Newly diagnosed	26
Known cases	116
Total	142
Duration of hypertension (years), mean±SD	5.31±4.86
SBP, mean±2SD	142.96±28.31
<140 (mm of Hg)	24/142
DBP, mean±2SD	94.90±29.50
<90 (mm of Hg)	42/142
MBP, mean±2SD	111.01±25.24
<107 (mm of Hg)	46/142
Treatment modality (*n*)	
ACEI users (enalapril)	97
CCB users (amlodipine)	51
ACEI plus CCB users	6
Risk factor-prevalence (*n*)	
Diabetes mellitus	29
Hyperlipidemia	7
Smoking	53
Alcoholism	31
Cardiac disease	6
Positive family history	67
Neurotoxic drug exposure	0

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

Table 2: Comparison of QTc values between newly diagnosed hypertensives (duration <6 months) and age- and gender-matched known hypertensives (13 males and 13 females, 26 in total in each group)

Parameter	Newly diagnosed cases	Matched known cases	*P*
Age, mean±2SD	37.19±13.14	35.19±15.98	0.33
QTc quantitative			
Mean±2SD	0.44±0.06	0.42±0.06	0.04*
Normal (*n*)	15	7	0.048*
Abnormal (*n*)	11	19	

Odds risk for abnormal qualitative QTc=3.70, 95% CI=1.16-11.86, *P*=0.03. *Statistical significance. SD=Standard deviation, CI=Confidence interval

Table 3: Comparison of QTc for heart rate values between age- and gender-matched subgroups of known hypertensives (duration >1 year) based on disease duration (26 males and 13 females, 39 total in each group)

Parameter	Duration ≤5 years	Duration >5 years	*P*
Age, mean±2SD	42.79±9.46	42.79±9.22	>0.99
QTc			
Mean±2SD	0.43±0.06	0.44±0.08	0.36
Normal (*n*)	18	23	0.36
Abnormal (*n*)	21	16	

SD=Standard deviation

Table 4: Comparison of QTc values between calcium channel blocker user hypertensives and age, gender, disease duration matched angiotensin-converting enzyme inhibitor user hypertensives (29 males and 22 females, 51 in total in each group)

Newly diagnosed cases at baseline			
Parameter	**CCB users *n*=4**	**ACEI users *n*=22**	***P***
Age, mean±2SD	31.5±12.48	35.86±16.40	0.33
QTc			
Mean±2SD	0.42±0.02	0.42±0.06	0.80
Normal (*n*)	3	16	1.00
Abnormal (*n*)	1	6	
After treatment of 1-5 years			
Parameter	**CCB users *n*=26**	**ACEI users *n*=48**	***P***
Age, mean±2SD	40.35±14.24	41.17±11.80	0.14
QTc			
Mean±2SD	0.43±0.06	0.44±0.08	0.37
Normal (*n*)	15	25	0.81
Abnormal (*n*)	11	23	
In total			
Parameter	**CCB users**	**ACEI users**	***P***
Age, mean±2SD	40.80±13.34	40.80±13.34	1.00
Duration, mean±SD	6.79±5.22	5.80±4.45	0.30
QTc			
Mean±2SD	0.43±0.06	0.44±0.06	0.37
Normal (*n*)	28	24	0.55
Abnormal (*n*)	23	27	

Odds risk for abnormal QTc=0.73, 95% CI=0.33-1.59, *P*=0.43.
SD=Standard deviation, ACEI=Angiotensin-converting enzyme inhibitor, CCB=Calcium channel blocker, CI=Confidence interval

Table 5: Correlation of QTc with blood pressure in study group

Variable	Statistic	SBP	DBP	MBP
QTc	*r*	−0.07	−0.11	−0.11
	P	0.38	0.20	0.19

SBP=Systolic blood pressure, DBP=Diastolic blood pressure, MBP=Mean blood pressure

DISCUSSION

Every third urban Indian is suffering from hypertension,[2] an iceberg disease that is going to double in number by 2025 as compared to 2000.[14] Patients with hypertension are at increased risk of developing a variety of cardiac structural and functional changes, prolonged ventricular repolarization being one of them.[3] It is unnoticed until screened by tool such as QTc interval and may progress to sudden cardiac death.[15] It definitely is an independent risk factor for cardiovascular morbidity and mortality.[16] In unpublished part of this study, we found that QTc prolongation was increased by age with a female disadvantage (prolonged QTc) but unaffected by current blood pressure. Hence, we tried to match hypertensives in our study by age, sex, and if possible duration of disease. By this paper, we have presented effect of disease duration, treatment, and associated risk factors on QTc interval in young hypertensives.

Results showed quantitatively higher QTc value and qualitatively high prevalence of prolonged QTc interval in new hypertensives (duration <6 months) as compared to age-, sex-matched known hypertensives, in line with the previous studies.[17,18] Due to asymptomatic nature, raised blood pressure remains unnoticed and without correction of the same repolarization abnormality can flare owing to LVH. Despite 33% prevalence of hypertension in urban India, only 42% are treated for the same,[2] and the majority of undiagnosed, like the newly diagnosed cases of our study group, forming submerged part of the iceberg, is left at risk of abnormal outcomes of hypertension.

Once diagnosed, hypertensives are offered antihypertensive therapy which by pressure control can benefit the repolarization abnormality. Calcium and angiotensin II are therapeutic targets against hypertension,[19] and our case group was taking predominantly monotherapy in the form of CCB or ACEI, both of which are known for cardiac structural remodeling.[9] There are studies showing benefit of ACEI therapy on regressing ventricular hypertrophy in short term[9] as well as on long run.[20] However, CCBs that do regress aortic hypertrophy[21] are not proven beneficial with reference to the prevention of repolarization abnormality.[22] This could be the cause why ACEI users had slight advantage as compared to matched CCB users in QTc values. ACEI or CCB can prevent target organ damage only if blood pressure is maintained,[23] which was not so in most of the cases in our study, like most other Indian hypertensives.[2] Only one-fifth Indian hypertensives have pressure control,[2] and this might explain why hypertensives with duration 5 years do not differ much in QTc value than those with duration more than 5 years. Another fact is that pressure control has no curative effect on QTc,[24] and the studies have proved that QTc prolongation is seen despite antihypertensive therapy,[25] even before LVH[26]

Table 6: Comparison of effect of the presence of individual coexisting risk factor on QTc values between matched subgroups (equal in number and similar in gender distribution) of hypertensives

Risk factor	Age (mean±2SD)	Quantitative variables		Qualitative variables (*n*)		Risk calculated	
		Duration (mean±SD)	QTc value (mean±2SD)	QTc prolonged	QTc normal	OR	95%CI
Diabetes (*n*=29)							
Present	42.38±5.36	5.76±4.44	0.44±0.03	16	13	7.69	2.13, 27.79
Absent	42.25±5.88	5.17±4.93	0.42±0.03	4	25		
P	0.94	0.67	0.0139*	0.0020*		0.0018*	
Smoking (*n*=53)							
Present	40.78±6.17	6.17±4.66	0.43±0.05	40	13	2.75	1.20, 6.28
Absent	40.45±6.68	5.70±4.71	0.43±0.03	28	25		
P	0.80	0.61	0.50	0.0253*		0.0165*	
Alcohol (*n*=31)							
Present	41.26±7.33	6.32±5.38	0.44±0.05	14	17	1.14	0.42, 3.11
Absent	41.06±7.49	6.39±5.16	0.42±0.03	13	18		
P	0.92	0.96	0.30	1.00		0.80	
F/H of HTN (*n*=67)							
Present	40.66±7.71	5.85±6.21	0.44±0.05	36	31	2.54	1.26, 5.15
Absent	40.84±6.21	4.91±4.60	0.42±0.03	21	46		
P	0.88	0.32	0.0057*	0.0141*		0.0094*	

*Statistical significance. OR=Odds ratio, CI=Confidence interval, SD=Standard deviation, FH= family history, HTN=hypertension

and in the absence of LVH.[16] Later, two facts justify the exclusion of use of the ECG LVH voltage criteria or echo measurement. This further reinforces the use of QTc screening among hypertensives and appropriate use of preventive pharmacotherapy such as β-blockers if required, which was offered to none in our study group.

In the presence of diabetes, QTc abnormality was significantly increased, in line with the previous studies,[8,27] and this can be explained by hyperglycemia-induced alteration. Half of cases had hypertension and diabetes together with poor glycemic control as seen in our previously published study,[28] so both chronic conditions have to be tackled simultaneously. Optimum blood pressure and glycemic control are required when both diseases are coexisting to lessen not only cardiovascular but also other risks. Hypertensive smokers similarly had significantly higher QTc prolongation which is well supported by other study,[29] same being true for alcoholism, but results were insignificant. The presence of positive family history too affected QTc interval adversely, but unlike diabetes, smoking, or alcoholism it is not modifiable. High prevalence of these four risk factors may partly explain high prevalence of prolonged QTc interval despite ACEI or CCB therapy. As mean age of hypertensives was 40 years, modification of these risk factors by appropriate interventions is of significance.

Given, the high prevalence of hypertension in India,[6] blood pressure assessment in all adults at every opportunity is both prudent and justified. QTc screening similarly can be used optimally that requires no expertise with cost-effectiveness. Adding QTc value improves risk stratification in hypertensive patients, helps to identify at risk subjects, and to guide appropriate preventive therapy for cardiovascular events such as arrhythmias. In line with this, strict blood pressure control and management of risk factors along with lifestyle modifications are felt needs. This can be accomplished even at primary health-care level, and the diseased must be offered primary prevention.

Limitations of study

The study was limited by small sample size, manual method of measuring of QTc interval, and presence of confounding factors which cannot be negated. Due to cross-sectional nature, it could not establish cause-effect relationship with certainty and effects of antihypertensive treatment cannot be totally justified without a prospective study. However, this study definitely warrants further work in this direction and suggests blood pressure screening, optimum use of a tool like QTc interval, and population-based approach to combat hypertension and its effects.

CONCLUSION

Young hypertensives on monotherapy with poor pressure control showed prolonged QTc interval, more so if newly diagnosed, not differing further after 1 year, whether using ACEI or CCB, with risk that is increased by the presence of diabetes, smoking, and positive family history. Early detection of hypertension, strict blood pressure control, QTc screening for repolarization abnormality, use of preventive pharmacotherapy, and lifestyle modification are suggested to minimize hypertension-induced cardiac repolarization abnormalities and its aftermaths.

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Conflicts of interest
There are no conflicts of interest.

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