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REVIEW

Modulation of the QT interval duration in hypertension with antihypertensive treatment

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The duration of the QT interval as measured by 12-lead electrocardiography is a measure of myocardial repolarization and is widely used to describe cardiac abnormalities, to determine the presence of cardiac toxicity and to evaluate drug safety. In hypertension, the QT interval is a predictor of the risk of both coronary events and cardiovascular death, after adjusting for the effects of additional risk factors. The mechanism of QT interval prolongation is multifactorial and includes cardiomyocyte hypertrophy and increased left ventricular mass, with accompanying changes in left ventricular transmural dispersion of repolarization, as well as changes in the tone of the autonomic nervous system of some patients with hypertension and mechano-electrical feedback, although this mechanism is less likely. Antihypertensive drugs vary in their effect on QT interval duration. The mechanisms underlying their effect depend on changes in left ventricular mass and autonomic nervous system tone, as well as changes in the activity of cardiac ion channels. Although blood pressure reduction is the primary goal of antihypertensive drug therapy and although the choice of antihypertensive drug treatment regimens varies among different individuals, the data regarding the disparate effects of antihypertensive drugs on the duration of the QT interval warrant consideration when implementing long-term pharmacotherapy for hypertension.
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INTRODUCTION

Abnormalities of ventricular repolarization are an important component of both ECG diagnostics and medical decision-making. The duration of the QT interval as measured by 12-lead electrocardiography is a measure of repolarization and is widely used to describe cardiac abnormalities, to determine the presence of cardiac toxicity or to evaluate drug safety.[1–6] QT interval duration is a predictor of the occurrence of cardiovascular events,[7–11] and increased QT duration is associated with the risk of sudden cardiac death in the hypertensive population, even among individuals without clinically recognized cardiac disease.[12] The increased risk of cardiovascular events, including sudden cardiac death, is a well-described consequence of sustained arterial hypertension.[13] Even small, non-specific abnormalities of repolarization may increase the risk of cardiovascular events in the hypertensive population.[14]

In subjects with uncomplicated hypertension, a prolonged QT interval (corrected for heart rate) carries a twofold increase in the risk of coronary events and cardiovascular death, after adjusting for the effects of age, sex, diabetes mellitus, serum cholesterol level, serum creatinine level, smoking, left ventricular hypertrophy (LVH) and 24-h systolic blood pressure (BP).[15] In a hypertensive population with electrocardiographic LVH, an analysis of maximum QT intervals identified persons at an increased risk for cardiac mortality despite effective BP-lowering treatment.[9] Prolonged QT intervals are a marker of cardiovascular morbidity and mortality in patients with resistant hypertension, even after taking into account traditional cardiovascular risk factors, including both hypertension and LVH.[16] The question arises as to whether hypertension modulates the QT interval and therefore accounts for a mechanism by which hypertension increases the likelihood of the occurrence of fatal cardiac events despite the effects of antihypertensive agents on the QT interval.

THE ELECTROPHYSIOLOGICAL BASIS OF THE QT INTERVAL

The electrophysiological basis of the QT duration is the duration of the action potential of a single ventricular cardiomyocyte, as well as the presence of electrical heterogeneity in the form of either transmural or trans-septal dispersion of ventricular repolarization in an intact heart.[17] An increase in duration of the QT interval may reflect an increase in the duration of the action potential in specific regions of the ventricle. Such increases reflect either an increase in inward current or a decrease in outward current.[18] Most drugs that cause an increased QT interval duration prolong cardiomyocyte action

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potentials by blocking potassium channels.[19] The potassium channels responsible for both the rapid (I_{Kr}) and the slow (I_{Ks}) activating components of the delayed rectifier potassium currents, in particular, modulate cardiac repolarization and have been implicated in both long QT syndrome and other forms of arrhythmia.[20]

In hypertension, the QT interval is viewed as a non-specific marker of cardiac pathology. The underlying cause of the prolongation of cardiac repolarization in hypertension remains controversial and reflects a large number of cardiac physiologic and pathophysiologic conditions. The dependence of the duration of the repolarization on the activity of potassium channels and potassium currents suggests that potassium currents should figure prominently in the relationship between the QT interval and hypertension. Interestingly, there is very little data regarding the relationship between QT and hypertension; however, the data suggest that a relationship between K_{ATP} channel polymorphisms and left ventricular size exists among hypertensive individuals.[21]

THE MECHANISMS UNDERLYING THE EFFECT OF HYPERTENSION ON THE QT INTERVAL

Left ventricular hypertrophy

Electrical remodeling in the setting of essential hypertension, as well as the consequent development of LVH, likely contributes to the pathophysiology of cardiac arrhythmias.[22] From a clinical perspective, it may translate into a propensity for individuals to suffer sudden cardiac death.[23,24] Increased left ventricular mass (LVM) is associated with changes in cardiac repolarization.[25–27] Several measures of cardiac repolarization, including QT duration, QT duration corrected for heart rate (QTc), QT variability and QT dispersion (the interlead differences in the duration of the QT interval) are associated with hypertensive heart disease, suggesting that increased LVM may modulate any QT parameter. Two decades ago, QT dispersion was enthusiastically studied as if it were an electrophysiological *holy grail* that explained the impacts of either diseases or drugs on the heart.[28] Previous investigations describing QT abnormalities in the hypertensive population focused primarily on QT dispersion, whereas others focused on QT duration. As the two phenomena are linked by their relationship with both LVH and BP in the majority of studies,[8,25–27,29–36] they will be discussed together in this review.

Piccirillo and colleagues[37] described their findings of QT abnormalities in hypertensive subjects with LVH and speculated that greater ventricular mass results in decreased repolarization synchronization in myocardial cells. This may explain not only the QT interval prolongation observed in previous studies but also the increased QT dispersion noted in said studies;[8,25–27,32,38–40] however, clear evidence confirming this interesting hypothesis is lacking. Another explanation for the relationship between QT changes and LVH is that cardiomyocyte hypertrophy is often associated with changes in either the expression or the activity of ion channels (primarily potassium and calcium channels). These changes may affect the action potential durations[41] and include specific alternations such as decreased potassium currents, dysregulation of intracellular calcium and gap junction dysfunction.[42–44] Other factors may contribute to QT prolongation in the setting of LVH, including fibrosis, myocardial ischemia and diabetes mellitus.[45,46]

Although LVH is an important factor in numerous cardiac diseases, several studies have noted the presence of QT prolongation in hypertensive patients, both with LVH and without LVH,[37,39] although this issue remains controversial.[40] Uncomplicated hypertensive patients may have increased cardiac mass;[47] therefore, the link between LVM and the QT interval may exist prior to the development of LVH. Experimental models have confirmed the presence of QT prolongation in the setting of hypertension, particularly in spontaneously hypertensive rats and models of both essential hypertension and LVH.[3,48,49] It remains unclear when hypertension-induced increases in LVM and QT prolongation begin to manifest, and the extent to which other factors such as cardiac fibrosis, diabetes mellitus or ischemic heart disease accelerate the changes in the QT interval in the setting of LVH.

Changes in the duration of the QT interval secondary to alterations of the autonomic nervous system in the setting of hypertension

Prolongation of the QT interval has been linked to both alterations in sympathetic drive[50] and imbalances of the autonomic nervous system.[33,51] Systemic catecholamines may alter ventricular repolarization[52] and prolong the duration of the QT interval, and also increase QT dispersion, even among healthy subjects.[52,53] The regulation of the QT interval by the autonomic nervous system has been demonstrated by several studies. Despite their comparable BPs, hypertensive patients with anxiety exhibit significantly longer QT intervals and broader QT dispersion than their counterparts without anxiety.[33] This finding is supported by evidence that the magnitude of beat-to-beat QT variability is related to cardiac sympathetic activation in hypertensive patients.[47]

Marfella and colleagues[54] determined that both the prolongation of cardiac repolarization and morning sympathetic overactivity coexist in hypertensive patients at the time of each patient's maximum morning BP. Interestingly, subjects with essential hypertension and increased LVM exhibited increased QT durations primarily during the awake period, including the time period during which morning catecholamine levels and BP were each elevated, but not later in the day or at night. The reason for these findings is complex because not all individuals with hypertension exhibit increased catecholamine synthesis and release, nor are they as sensitive to the effects of catecholamines on the heart.[55,56]

Changes in QT interval duration secondary to acute alterations in BP

In experimental hypertension, elevated BP correlates with QT prolongation independent of associated LVM.[3] This finding suggests that ventricular loading may affect ventricular repolarization. Indeed, decades ago, a mechano-electrical feedback mechanism[57,58] was implicated in action potential duration disturbances.[59] The experimental data were confusing, however. Although, there appears to be agreement that mechano-electrical feedback modulates action potential duration in muscle preparations, this phenomenon may not apply to the entirety of the heart.[58] Moreover, Dean and Lab[57] demonstrated that BP reduction with nitroprusside is associated with increased action potential durations, a finding that opposes the contention that BP elevation prolongs the durations of action potentials. However, it has been suggested that the dynamicity of the duration of the QT interval is influenced by circadian BP patterns.[60] It is widely known that circadian rhythms are involved in BP regulation.[61] Moreover, Marfella and colleagues[54] demonstrated that QT duration increases in conjunction with morning BP peaks in hypertensive individuals. Following chronic antihypertensive drug therapy, subsequent decreases in BP may be more strongly associated with reductions in the QT interval, as well as small decreases in LV mass.[62] Given the controversy surrounding the experimental data,[58] the mechanism underlying changes in the duration of the QT interval secondary to alterations in BP remain to be elucidated.

Table 1 The effect of inhibitors or antagonists of the renin angiotensin system on QT interval in clinical studies

Authors	*Drug*	*Patient type*	*Sample size*	*Type study*	*Follow up*	*Effect on QT*	*Effect on QTc*	*Effect on QTc disp.*	*References*
Gonzalez-Juanatey *et al.*	Enalapril	HTN and LVH	24	Observ.	7 years	Reduction	Reduction	—	30
Lim *et al.*	Irbesartan	HTN	106	Randomized, multicenter, double-blind	6 months	Reduction	Reduction	Reduction	31
Oikarinen *et al.*	Losartan	HTN and LVH	317	Multicenter, double-blind, double-dummy, randomized, prospective, active-controlled parallel group study	1 year	Reduction	Reduction	Reduction	32
Fogari *et al.*	Aliskiren	HTN and DM	170	Prospective, randomized, open label, blinded-end point, parallel group study	12 and 24 weeks	Reduction	Reduction	Reduction	68
Malmqvist *et al.*	Irbesartan	HTN and LVH	115	Randomized, double-blind, crossover, single-center, placebo-controlled study	48 weeks	Reduction	Reduction	Reduction	69
Porthan *et al.*	Losartan	HTN	183 men	Randomized, double-blind, crossover, single-center, placebo-controlled study	4 weeks	Reduction	Reduction	Reduction	70

Abbreviations: DM, diabetes mellitus; HTN, hypertension; LVH, left ventricular hypertrophy; Observ., observational study; QTc, corrected QT.

THE EFFECT OF ANTIHYPERTENSIVE AGENTS IN THE MODULATION OF THE DURATION OF THE QT INTERVAL

The ability of certain pharmacologic agents to alter the QT interval is well accepted.[6,19,63,64] Specific agents, primarily antiarrhythmic drugs, are able to reduce the duration of the QT interval via different pharmacological mechanisms.[65,66] The potential for antihypertensive drugs to alter the QT interval must be considered within the context of the effect of BP reduction on LV mass, as well as the effects of specific drugs on the autonomic nervous system, which in turn affects the duration of the QT interval and exerts additional effects on the heart. As suggested above, if LVH produces changes in the duration of the QT interval, one may expect that a reduction in LVM that coincides with a sustained BP decrease will be important in decreasing the duration of the QT interval. Indeed, the LIFE study demonstrated that antihypertensive therapy reduced the QT interval and suggested that this occurred exclusively in patients who experienced a concomitant reduction in their echocardiographic LVH.[32] LVH regression secondary to antihypertensive drug therapy has also been associated with a reduced QTc dispersion and QTc variability, which some investigators have linked to the development of cardiac arrhythmias.[67] Antihypertensive drugs are not equivalent in their modulation of the QT interval despite similar antihypertensive (that is, BP reducing) and antihypertrophic (that is, cardiac mass reducing) medications.

These discordances between drugs and their ability to reduce BP and affect changes in the QTc interval have been reported clinically in hypertensive populations,[31,67–70] and have been documented in animal models of hypertension.[3] Another consideration is that the time course for changes in the QT interval is different than those regarding changes either in LV mass or in BP. Chronic treatment with the angiotensin-converting enzyme inhibitor (ACEi) enalapril elicited a significant reduction in BP following 8 weeks of treatment; a reduction in LVM was evident following 1 year of treatment, and a reduction in the duration of the QT interval was evident following 3 years of treatment.[30] These findings suggest that hypertrophy may prolong the duration of an action potential; however, its regression may not immediately result in AP normalization.[71]

In a comparative study involving amlodipine and irbesartan, both drugs decreased BP, but only irbesartan decreased the duration of the QT interval.[31] Interestingly, a positive correlation between decreased BP and decreased QT duration was noted in this study. Similar results were described by Fogari *et al.*[68] in hypertensive patients with type 2 diabetes mellitus, without LVH on echocardiography. Despite similar BP-lowering effects, the direct renin inhibitor aliskiren, but not the calcium channel blocker (CCB) amlodipine, decreased the duration of the QT interval in these patients. Therefore, pharmacotherapies with similar effects on hypertension will not exert identical effects on cardiac repolarization. When considering the effects of antihypertensive treatment, we must consider not only their effects on BP and LVH but also their effects on the rest of the body. Beta-blockers (BB), ACEi and angiotensin receptor blockers (ARB) may affect the sympathetic system, and may therefore potentiate the positive effects of BP control and LVM reduction. Diuretics may affect electrolyte balance,[72] which impacts the QT interval. Dihydropyridine CCB may potentially activate the sympathetic nervous system;[73] therefore, the positive effects exerted by this medication on BP may be masked by its additional pharmacological effects.

ACE inhibitors and ARBs

The majority of studies have provided evidence that drugs inhibiting the renin-angiotensin-aldosterone system, particularly ACEis and ARBs, exert beneficial effects on the duration of the QT interval (Table 1). These drugs reduce the QT interval.[30–32,69,70] Experimental studies have also demonstrated that ACEis reduce the QT interval.[1,3,48,74] The effects of either an ACEi or an ARB on the QT interval are exerted via mechanisms that regulate also the QT interval. The effects of ACEis and ARBs on cardiac hypertrophy and cardiac fibrosis may have proven to be important effects.[75–78] ACEis and ARBs may affect the electrophysiological mechanisms altered by angiotensin.[79] The inhibitory effect exerted by angiotensin II on the rapidly activating components of delayed rectifier potassium current (I_{Kr}) has been described previously and may result in prolonged action potential duration.[80]

One of the principal mechanisms that contributes to cardiac electrical disturbances is the dysregulation of intracellular calcium cycling.[81] The intracellular calcium within the sarcoplasmic reticulum is released via ryanodine receptors (RyR2) during systole and is restored during diastole via the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA2a) pump.[82] In heart failure, that is, at a high angiotensin II state, both SERCA2a and RyR2 are suppressed.[83,84] The decrease in SERCA2a activity, which is triggered by angiotensin II, may lead to increased diastolic calcium and arrhythmogenesis. Indeed, this effect has been described previously in the setting of various pathological conditions, including hypertensive cardiomyopathy, in which the administration of either ACEIs or ARBs normalizes the abnormal intracellular calcium handling and increases SERCA2a

Table 2 Effects of beta-blockers on QT duration evaluated in clinical studies

Authors	Drug	Patient type	Sample size	Type study	Follow-up	Effect on QT	Effect on QTc	Effect on QTc disp.	References
Galetta *et al.*	Nebivolol	HTN and LVH	25	Observ.	4 weeks	Reduction	Reduction	Reduction	29
Malmqvist *et al.*	Atenolol	HTN and LVH	115	Randomized, double-blind, crossover, single-center, placebo-controlled study	48 weeks	Prolongation	Reduction	Non-signif.	69
Porthan *et al.*	Bisoprolol	HTN	183 men	Randomized, double-blind, crossover, single-center, placebo-controlled study	4 weeks	Reduction	Reduction	Reduction	70

Abbreviations: HTN, hypertension; LVH, left ventricular hypertrophy; Non-signif., no significant effect; Observ., observational study; QTc, corrected QT.

expression.[85,86] Whether these ACEis or ARBs antagonize the effect of angiotensin on SERCA2a remains unclear.

Aldosterone has been linked to cardiac hypertrophy with prolongation of the QT interval, as well as electrical instability. This has been explained by the downregulation of the potassium channels responsible for the repolarization currents (I_{to}, I_{K1}, I_{kur}), as well as the downregulation of L-type Ca^{2+} channels, which suggest that aldosterone exerts direct proarrhythmic effects.[87,88] Aldosterone antagonists, eplerenone in animals[87] and spironolactone in humans,[89] have been found to modulate the duration of the QT interval. Another contributing and potentially crucial mechanism of reducing the QT interval following ACEi and ARB therapy is the modulation of autonomic nervous system function by decreasing sympathetic drive. Angiotensin II modulates the autonomic nervous system via various mechanisms, including the release of catecholamines, the stimulation of both the systemic and the peripheral sympathetic nervous system, and the modulation of centrally regulated vagal tone.[31,90,91] Consequently, drugs reducing the influence of either angiotensin or aldosterone may exert significant benefits by reducing sympathetic drive and will likely also exert beneficial effects regarding QT interval regulation.

Beta-blockers

Both sympathetic drive and catecholamines alter the electrical activity of the ventricles via the modulation of repolarization,[53,92] and play a crucial role in the development of hypertension in specific patients with hypertension. Beta-adrenergic stimulation prolongs the QT interval in some cases as a result of the induction of myocardial ischemia.[5] Beta-blockade may also decrease the duration of the QT interval and normalize ventricular repolarization in a dose-dependent manner, without having any effect on either LVM or BP.[29,93,94]

Although the effects of beta-blockade on the QT interval in the setting of long QT syndrome appears to be minimal,[95] previous studies have suggested that the potential of this drug class to reduce the QT interval may also benefit hypertensive patients (Table 2). Particularly, clinical studies involving carvedilol,[96] atenolol[69] and nadolol,[97] as well as bisoprolol,[70] demonstrated effects in patients with prolonged QT intervals. Carvedilol and its analogues, in particular, may have additional antiarrhythmic properties.[98,99] Its modulation of cardiac electrogenesis appears to be complex, and may be related to a combination of beta-blocking effects and the modulation of a variety of ion channels (including the direct inhibition of ryanodine receptors) and currents. Additionally, this hypothesis appears to be supported by its antioxidant, antiischemic and antihypertrophic effects.[100] Controversially, some experimental studies in the past demonstrated QT prolongation following the administrations of BBs.[101,102] The ability of BBs to shorten the duration of the QT interval, which has made possible their use in the treatment of long QT syndrome,[103] strengthens the case that BBs reduce the duration of the QT interval. The QT-modulating actions of BB may be an additional benefit that complements their antihypertensive effects.

Calcium channel blockers

Dihydropyridine CCBs do not appear to exert a beneficial effect on QT interval duration (Table 3). Historically, the CCB bepridil is known to carry risks of both QT prolongation[104] and the potentially fatal arrhythmia *torsade de pointes*.[105] This may be the result of its concomitant actions on potassium channels.[36,105] There is some clinical evidence that dihydropyridine CCBs may prolong the QT interval in subjects with normal sinus node function;[106] experimental data support this finding.[3] When comparing various antihypertensive treatments in a hypertensive population, CCBs often fail to reduce cardiac repolarization abnormalities despite their ability to reduce both BP and LVH[31,68,70,107] and may actually trigger QT prolongation and subsequent arrhythmias in hypertensive subjects.[108]

CCBs mediate their antihypertensive effects via vasodilatation by blocking the L-type calcium channels found in smooth muscle cells. However, their overall beneficial efficacy may be significantly decreased by counter-regulatory cardiac and renal activation because of baroreflex mechanisms.[109] Therapy with dihydropyridine CCBs increases norepinephrine plasma concentrations, although differences in intensity have been described when comparing particular agents and formulations.[73,109–112] De Champlain *et al.*[110] observed a transient increase in norepinephrine levels with a slow-release nifedipine preparation, and a sustained increase in norepinephrine levels following chronic treatment with amlodipine, suggesting the existence of differences in sympathetic activation between the two preparations. Similarly, Leenen *et al.*[112] noted that extended release felodipine significantly increased supine and standing plasma noradrenaline, which was not observed with either sustained release nifedipine or the ACEi enalapril. The interaction between CCBs and the sympathetic and parasympathetic nervous systems is also important. Karas *et al.*[113] reported increased sympathetic activity during the day and decreased parasympathetic activity during the night following therapy with amlodipine; an effect that correlated with increased plasma norepinephrine levels. In contrast, the ARB telmisartan increased parasympathetic activity without affecting the norepinephrine levels during both the night and the day, whereas ramipril increased parasympathetic activity only during the day.[114] Only CCBs that elicit a concomitant blockade of the N-type calcium channels located at sympathetic nerve endings, which enables them to directly inhibit sympathetic neurotransmitter release and suppress sympathetic activity, may avoid reflex activation.[114,115] Interestingly, only these CCBs may successfully decrease cardiac repolarization.[116]

Table 3 Effects of calcium channel blockers on QT duration evaluated in clinical studies

Authors	Drug	Patient type	Sample size	Type study	Follow-up	Effect on QT	Effect on QTc	Effect on QTc disp.	References
Lim *et al.*	Amlodipine	HTN	106	Randomized, multinational, multicenter, double-blind	6 months	Non-signif.	Non-signif.	Non-signif.	31
Fogari *et al.*	Amlodipine	HTN and DM	170	Prospective, randomized, open label, blinded-end point, parallel group study	12 and 24 weeks	Non-signif.	Non-signif.	Non-signif.	68
Porthan *et al.*	Amlodipine	HTN	183 men	Randomized, double-blind, crossover, single-center, placebo-controlled study	4 weeks	Non-signif.	Non-signif.	Non-signif.	70
van Wijk *et al.*	Isradipine *i.v.*	HTN	25	Observ.	30 min	Prolongation	Prolongation	—	106
Lind *et al.*	Diltiazem	HTN	24	Observ.	6 months	Prolongation	—	—	119

Abbreviations: HTN, hypertension; LVH, left ventricular hypertrophy; Non-signif., no significant effect; Observ., observational study; QTc, corrected QT.

Table 4 Effects of diuretics on QT duration evaluated in clinical studies

Authors	Drug	Patient type	Sample size	Type study	Follow-up	Effect on QT	Effect on QTc	Effect on QTc disp.	References
Porthan *et al.*	Hydrochlorothiazide	HTN	92	Randomized, double-blind, crossover, single-center, placebo-controlled	4 weeks	Non-signif.	Non-signif.	Non-signif.	70
de Gregorio *et al.*	Furosemide and citalopram	HTN and major depression and hypokalemia	1	Case study	—	prolongation (+ *Torsade de Pointes*)	prolongation	—	130
Letsas *et al.*	Indapamide and prednisolone	HTN and SLE	1	Case study	—	—	Prolongation (+*Torsade de Pointes*)	—	131
Mok *et al.*	Indapamide	HTN and hypokalemia and hyponatremia	1	Case study	—	—	prolongation (+ type 1 Brugada ECG pattern)	—	132
Wang *et al.*	Indapamide	HTN and LQTS and mild hypokalemia	1	Case study	—	prolongation (+ syncope)	prolongation	—	133

Abbreviations: HTN, hypertension; , LQTS, long QT syndrome; LVH, left ventricular hypertrophy; Non-signif., no significant effect; Observ., observational study; QTc, corrected QT; SLE, systemic lupus erythematosus.

An alternative explanation for unfavorable effects of CCBs on repolarization is their possible effects on potassium channels, as dihydropyridines not only suppress Ca^{2+} entry but also exert inhibitory effects on potassium channels.[117,118] By contrast, the nondihydropyridine CCB verapamil shortened the duration of the QT interval, whereas diltiazem did not change the duration of the QT interval in the setting of angina pectoris,[104] and appeared to prolong the interval in a small sample of hypertensive patients[119] (Table 3). Verapamil significantly shortened the QT interval at low heart rates in patients with structural normal hearts within 2 months after oral verapamil was prescribed for paroxysmal atrioventricular nodal re-entrant tachycardia.[120] Verapamil reduces both the action potential duration and the transmural dispersion of repolarization via direct action on the heart,[121,122] as well as via central nervous system action, which mediates decreases in BP.[123] There is no evidence regarding the pro-arrhythmogenic potential of dihydropyridine CCBs. Any pro-arrhythmogenic risk is likely to be marginal, as the blockade of L-type calcium current ($I_{Ca,\,L}$) may subsequently reduce intracellular calcium release and early after-depolarization, and suppress ventricular arrhythmogenesis.[124,125] The antiarrhythmic effects of both verapamil and diltiazem are well known.

Diuretics

The effect of diuretics on the QT interval is complex. Some types of diuretics exert direct effects on the heart, as demonstrated by their actions in isolated cardiomyocytes,[126] and these effects may be observed in the setting of LVH.[127] Diuretics, particularly loop diuretics and thiazide diuretics, produce electrolytic disturbances such as hypokalemia and hypomagnesemia.[72] These electrolyte disturbances may result in QT interval prolongation. The potassium-sparing diuretic amiloride reduced both the duration of the QTc and dispersion, and increased serum potassium concentrations in patients with NYHA II-III.[128] Similarly, when added to an ACEi or an ARB, both spironolactone and amiloride shortened the QTc interval concomitantly to reduction of cardiac fibrosis and increased serum potassium levels in stroke survivors.[129] When comparing diuretics with other antihypertensive agents, they either exert no effect[70] or occasionally prolong repolarization[130,131] (Table 4). Indapamide[131–133] and furosemide[130] have each been associated with both QT prolongation and the subsequent development of *torsade de pointes* or Brugada syndrome or syncope. The net effect of diuretics on the duration of the QT interval is the net effect of their favorable actions on BP[32] and their effects on electrolyte homeostasis.

Centrally acting antihypertensive agents

Consistent with the evidence that sympathetic activity plays an important role in the regulation of the duration of the QT interval, central alpha-2 agonists would be expected to reduce the QT interval. However, only limited evidence supporting this exists in the literature. Clonidine attenuates QT prolongation in some experimental models

of rat[134] and rabbit,[135] and its effects on QT variability have been suggested in humans.[136] The relationship between these effects and BP remains questionable. Even less information is available regarding QT modulation by imidazoline receptor agonists (moxonidine, rilmenidine).

Direct vasodilators

Direct vasodilators may also have an influence on QT interval measurements,[34] but a link to their BP-lowering effects is missing. Nicorandil, in particular, shortens ventricular repolarization if prolonged experimentally[137] and modulates QT interval changes in humans.[35,138] However, nicorandil acts directly on ATP-sensitive K^+ channels; this action is predictable and is likely not associated with BP changes.

CONCLUSION

The observation that a prolonged QT interval (corrected for heart rate) increases the risk of both coronary events and cardiovascular death in hypertensive patients, even after adjusting for the effects of other cardiovascular risk factors,[15] should serve as an incentive for clinicians to focus their attention on the QT interval in the assessment of hypertension. The mechanism underlying QT interval prolongation is multifactorial and includes cardiomyocyte hypertrophy, increased LVM, with consequent changes in left ventricular transmural dispersion of the repolarization, as well as changes in autonomic nervous system tone in patients with hypertension, and less likely a mechano-electrical feedback. Although BP reduction is the primary goal of antihypertensive drug therapy, and the type of antihypertensive drug treatment varies in different individuals, the data regarding the disparate effects of antihypertensive drugs warrant consideration when planning long-term pharmacotherapy for hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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