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# Effects of Drugs on Electrocardiogram: A Review

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## Abstract

The use of the antiarrhythmic drug is common to treat heart disorder. A computational modeling and simulation are promising tools that could be used to investigate the effects of drugs on cardiac electrophysiology. Aim of this paper is to review the effects of different drugs on cardiac electrophysiology. Effects of sotalol, atenolol, amiodarone, Lidocaine, digoxin, and dofetilide are shown in this paper. These drugs can prolong the QT interval of the electrocardiogram. This effect is important as it is associated with polymorphic ventricular tachycardia and sudden cardiac death. These drugs prolong the QT interval and induce torsade de points on ventricular repolarization. The result shows that the drugs produce the significant increase in QT interval dependent on dose.

**Keywords**: Torsade de points

## Introduction

The surface ECG analysis is widely used for the diagnostic of cardiac diseases. The ECG is a noninvasive technique that allows visualization of the heart's electrical activity. The changes in duration of the QT interval are related to certain pathologies and with the effects of different drugs. On the other hand, the duration of the QRS complex also gives information about the status of the myocardial conduction system. All this raise the necessity of making precise of these intervals of the ECG.

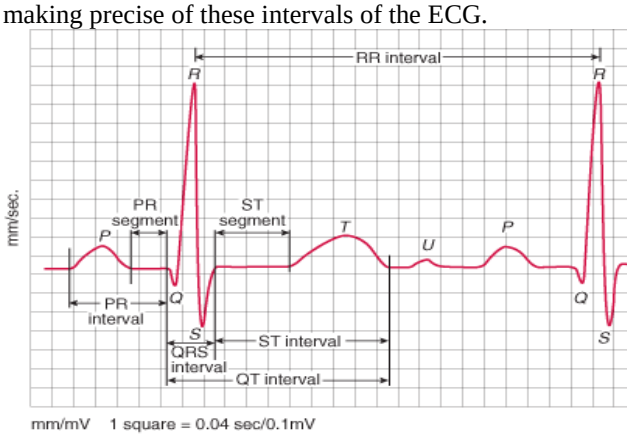


**Fig. basic electrocardiography http://www.sh.lsuhsc.edu/fammed/outpatientmanual/basicecg.htm**

The current standard in assesing the cardiac safety of new drug in clinical trials has centered on evaluiting ventricular repolarization duration,namely the QT interval.QT interval is measured from starting of the Q wave to termination of the T wave.it represents the duration between the onset of depolarization and the completion of the repolarization of the myocardium.

The QT interval is dependent on heart rate,age and gender. A QT interval of the 430ms is accepeted as the upper limit of normal for men and 450ms for women,and for the children upto age of 15 year is 440ms.[6]

**Mechanism of antiarrhythmic drug induced QT prolongation.**

The QT interval represents the cellular ventricular action potential and is the net result of coordinated function of various ionic currents. Na+ and Ca2+inward currents are primarily responsible for action potential upstroke and depolarization, whereas outward current K+ are responsible for myocyte repolarization. The abnormalities of depolarizing and repolarizing currents can dramatically change the duration of the action potential. Drug induced increases in depolarizing current and decreasing repolarizing currents will prolong the ventricular action potential duration and thus the QT interval.

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However the repolarization phase of the action potential is especially important in QT interval prolongation resulting from attenuated outward movement of potassium ions.

The two main subtypes responsible for ventricular repolarization are the 'rapid (Ikr)' and 'slow (Iks)'potassium currents. Blockade of either of these delayed rectifier K+ currents is associated with lengthening of the action potential. However Ikr is often more susceptible to drug effects that may manifest clinically as a prolonged QT interval and abnormalities on the surface electrocardiogram.[13]

**Early after depolarization**

The prolongation of repolarization may promote action potential instability with increased beat to beat variability of duration. Subsequently this may result in activation of premature inward depolarization currents known as an early after depolarization (EAD).EADs are generally considered to result from reactivation of the voltage dependent Ca2+ current with secondary depolarization of the cell. When EADs have sufficient amplitude, they may trigger another action potential and promote triggered activity. As results EADs, when accompanied by notably increased dispersion of repolarization, may induce re-entry and may be responsible for initiation of a tachycardia.[13]

**Dispersion of repolarization**

EADs are easily induced in a subset of myocardial cells from the mid ventricular myocardium know as M cells, and in the His-Purkinje network. In response to the Ikr blockade, M cells demonstrate more pronounced action potential prolongation compared with subendocardial and subpericardial cells. So it is possible that EADs may be responsible for initiation of a tachycardia, whereas dispersion of repolarization may be responsible for its perpetuation.[13]

Separation of the epicardial action potential from that of M cells during the final phase has represented on the ECG by the beginning of the T wave. Under the normal condition this separation is gradual such that the precise start of the T wave is difficult to determine. Final epicardial repolarization is proposed to correspond with the peak of the T wave, whereas final repolarization of the cells is consistent with the end of the T wave.[13]

## Method

They built device with a commonly available IBM PC. The ECG analog signal is issued from patient and connected on multichannel acquisition network. The system is used to acquire different signals and lead them to the PC-based supervision console using standard USB cable. They obtained digitized signal from the smart sensor which is built with a micro-controller including an analog to digital convertor.

The software allows both recording and on line treatment of the ECG.it gives more information to clinician.so ECG signal and heart rate continuously displayed on the screen of computer. Heart rate was measured from the RR intervals which are computed after QRS complexes detection and validation.[2]

**QRS detection**

After analog to digital conversion at the sampling rate of the 256HZ, the ECG signal samples are sent to special QRS detection algorithm which locates exactly the R peak.[2] It is based on the use of band-pass filter with a center frequency of 17 Hz. Adaptive thresholds are then used to detect the derivative direction changing and locate the R peak. In order to reject artifacts, the QRS wave is isolated taking 20 samples before and after the detected R peak.[2]

**ECG recoding protocol**

They were took the 200 patient for 24 hour of ECG recording. On the 1st day they observed 100 of patient on 24 hour ECG recording after treatment with β1-selective β blocking agent atenolol. 160mg of drug was given by mouth at 8 AM and recording were started at 10 AM.2nd day another 100 participants were subjected to 24 hour ECG recording after the treatment of sotalol with 160mg of dose.[4]

Duration of the QT interval was measured at the heart rates of 60,70,80,90,110 and 120 beats per minute. Heart rate had to be stable for 60sec. A variation of the ±5 beats per minute was allowed (e.g. heart rate could have been between 45 and 55 beats per minute can be accepted as heart rate of 50 beats per minute.)10 successive RR intervals were taken to measure heart rate.

**Effects of various drugs.**

***Effects of sotalol and atenolol***

The measured values of QT intervals at heart rates of 50, 60,70,80,90,100,110,120 beat per minute and correspondence value of QT interval shown in table.[4]

They measured the QT interval of patient when patient were awake and asleep at stable heart rate of 50 and 60 beats per minute, the interval was 405±17 msec while awake and 426±15 msec while asleep. At the heart rate of 60 beats per minute, the corresponding values were 388±16 and 406±17 msec respectively.[4]

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**Table-1: QT intervals in patients before and after atenolol and sotalol [4]**

| Heart rate (bpm) | No of patients | Before drug QT(ms) | After Atenolol QT(ms) | After Sotalol QT(ms) |
|---|---|---|---|---|
| 60 | 20 | 395±12 | 383±19 | 406±23 |
| 70 | 15 | 367±17 | 366±15 | 393±15 |
| 80 | 15 | 347±14 | 350±16 | 368±16 |
| 90 | 15 | 326±15 | 339±13 | 352±14 |
| 100 | 15 | 311±12 | 325±13 | 319±12 |
| 110 | 20 | 304±16 | 315±17 | 301±15 |

This mean waking heart rate before atenolol was 77±6 beats per minute. After atenolol it was 66±4 beats per minute. During the sleep the corresponding values of mean heart rate were 56±6 and 51±3 beats per minute respectively. Values of QT interval before and after atenolol and sotalol are shown in table. After the drug treatment QT interval were significantly longer at the heart rate of 90,100,110 beats per minute and significantly shorter at the heart rate of 60 beats per minute than before drugs.it has been shown that β blockade with propranolol causes no significant changes in QT intervals when heart rate held constant.in the study reported here acute treatment with β1 selective β blocking agent atenolol changed the dependence of the QT on the RR interval. The difference was greatest at heart rates between 90 and 110 beats per minute, when atenolol lengthen the QT interval.[4]

***Effects of amiodarone***

They used standard 12 lead ECG for continues monitoring of ECG. The clinical and demographic characteristic of the study population are presented in table1. The majority of the patient in the study had received antiarrhythmic drug therapy for the treatment of ventricular tachyarrhythmia occurring in the setting of chronic atherosclerotic heart disease. The demographic characteristic of patient with and without torsade de pointes is summarized in table 2.individual characteristics of patient who developed drug induced torsade de pointes are presented in table 3.quinidine was responsible for torsade de pointes in the majority of the patient.[3]

**Table-2: characteristic of patient with and without drug induced torsade de points. [3]**

| Characteristic | All patient | Patient with torsade de pointes | Patient without torsade de pointes |
|---|---|---|---|
| No. | 38 | 9 | 29 |
| age | 64±10 | 65±11 | 64±9 |
| Male (%) | 30(79) | 6(67) | 24(83) |
| LVEF | 0.39±0.16 | 0.31±0.13 | 0.41±0.16 |
| Heart disease (%) | | | |
| ASHD | 37(97) | 8(89) | 29(100) |
| other | 1(3) | 1(11) | 0(0) |
| Rhythm treated (%) | | | |
| VT/VF | 37(97) | 8(89) | 29(100) |
| AF | 1(3) | 1(11) | 0(0) |

LVEF: left ventricular ejection fraction, ASHD: atherosclerotic heart disease; VT: ventricular tachycardia; VF: ventricular fibrillation; AF: atrial fibrillation;

QT interval prolongation is associated with the development of torsade de pointes. [3] However in patients who have responded to antiarrhythmic drug therapy with excessive QT interval prolongation and torsade de points, subsequent amiodarone therapy typically prolong the QT interval to a comparable extent without precipitating torsade de pointes.

In this study they assessed the effects of class 1a antiarrhythmic drug and amiodarone on precordial QT interval dispersion in patient with and without class 1a drug induced torsade de pointes. The results shows a unique response of precordial ECG measure of ventricular repolarization times in patient who develop class 1a drug induced torsade de points. Such patient demonstrates prolongation of both single lead measure of ventricular repolarization time and precordial lead measures of dispersion of regional ventricular repolarizations time. However patient who do not develop class 1a drug induced torsade de pointes and patient receiving amiodarone therapy demonstrate prolongation of single lead measures of ventricular repolarization time. This disparate effect of class 1a drug therapy and amiodarone therapy on measures of dispersion of regional ventricular repolarization times occurs despite comparable prolongation of single lead measures of ventricular repolarization times.[3]

**Table-3: characteristic of patient with class 1a drug induced torsade de pointes. [3]**

| Patient | Age(year) | Drug | Exposure time(day) | QT(msec)baseline | QT(msec)on drug |
|---|---|---|---|---|---|
| 1 | 66/female | quinidine | 1 | 459 | 498 |

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| | | | | | |
|---|---|---|---|---|---|
| 2 | 66/male | quinidine | 2 | 431 | 604 |
| 3 | 54/male | quinidine | 2 | 477 | 535 |
| 4 | 71/male | quinidine | 4 | 519 | 558 |
| 5 | 71/male | quinidine | 4 | 485 | 711 |
| 6 | 71/male | quinidine | 10 | 401 | 512 |
| 7 | 61/male | quinidine | 60 | 457 | 493 |
| 8 | 43/female | procainamide | 9 | 473 | 514 |
| 9 | 78/female | disopyramide | 17 | 353 | 643 |

Class 1a antiarrhythmic drug therapy prolongs global measure of ventricular repolarization time, in patients who do not develop class 1a drug induced torsade de pointes; this effect is regionally homogenous as reflected in the absence of an increase in QT interval dispersion. However in patient who develops torsade de points, ventricular repolarization times are prolonged in a nonhomogeneous fashion accompanied by an increase in QT interval dispersion. [3]

***Effects of Lidocaine***

Lidocaine is a class 1b antiarrhythmic drug that acts blocking the fast sodium current. In this work they developed the mathematical model of Lidocaine effects has been developed. This model is incorporated to the luo Rudy model of guiea pig ventricular action potential and the effects of different basic cycle length (BCL) and concentration of drug on the action potential characteristics has been studied.[8]

In order to study the effects of Lidocaine on sodium current, they applied trains of stimuli at different BCLs and concentrations. Stimulation recording of sodium current (Ina), maximal upstroke velocity (Vmax), action potential duration (APD90) and conduction velocity (CV) are shown for different Lidocaine concentration. Fig 2 shows that Ina peak was -377µA/µF in normal condition, while in presence of Lidocaine the depression on Ina was evident. With a BCL of 300ms the Ina value reduced to -347 to -227µA/µF for concentration of 100 µM Lidocaine respectively. That means inhibitory effects on sodium current was around 8% and 39% respectively.[8]

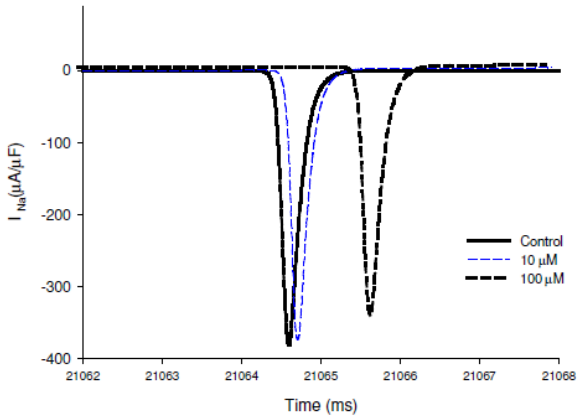


**Figure 2. Effects of Lidocaine concentration on Ina for a BCL 300ms [8]**

At a BCL 1000ms, the Ina was reduced to 2% and 17% for 10µM and 100µM respectively. The effects of Lidocaine on Vmax in figure 3. For 1µM the Vmax was reduced to a 3% while for 100 µM the reduction was of 22%.

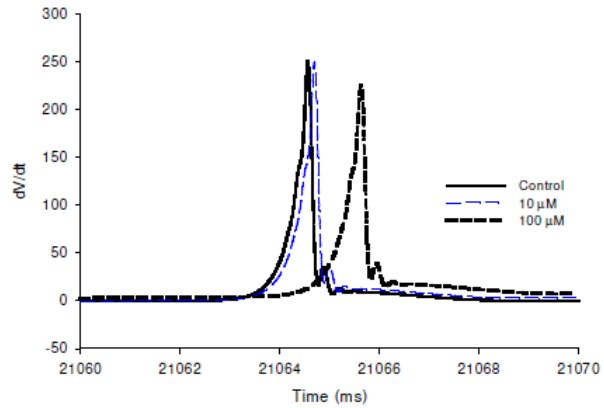


**Figure3. Effects of Lidocaine on maximal upstroke velocity of action potential for a BCL 1000ms.[8]**

In this study they have proposed a model to characterize the behavior of Lidocaine in ventricular cells of guinea pig. The model is based on experimental results and takes into account the experimental evidence that shows that the interaction of the drug with the channel occurs in inactivated state.

***Effects of digoxin***

The risk of the ventricular proarrhythmia from atrial defibrillation shocks depends on current being delivered to a portion of the ventricular myocardium at a time of vulnerability. The right atrium coronary sinus reduces lead configuration reduces both the total current delivery and the proportion reaching the ventricles, but it is still likely that a shock delivered during the ventricular vulnerable period could stimulate sufficient myocardium to initiate an arrhythmia. The vulnerable

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period generally falls within the latter portion of the T

| Baseline demographic | | | | |
|---|---|---|---|---|
| Age-years | 70 | 53-84 | 70 | 49-82 |
| Male-sex | 70% | 171 | 67% | 146 |
| Duration of heart failure.() | 9 | 0.07-144 | 12 | 0.07-96 |
| Current smoker (no) | 42% | 101 | 33% | 71 |
| Medical history(no) | | | | |
| Myocardial infraction | 55% | 135 | 56% | 123 |
| Ischemic heart diseases | 71% | 173 | 71% | 155 |
| Diabetes | 13% | 32 | 20% | 43 |
| hypertension | 16% | 0.5-1.2 | 17% | 37 |

wave, corresponding at a cellular level to the relative refractory period of the myocyte, and at a microscopic level to an interval when ventricle is in homogeneously excitable. Generally the shocks that are synchronized to the R wave are incapable of proarrhythmia. However at short cycle lengths the R wave may commence at a time when part of the ventricular myocardium is still only partially excitable.[5]

In the present study they were found that the mean waiting time increased almost exponentially with that present threshold, from under 10s with threshold of 400ms to 300-600ms with a threshold of 800ms.the mean for episodes on digoxin exceeded that for episodes occurring on placebo, for reasons that are unclear.at thresholds that are likely to be clinically used namely between 400ms and 600ms, the mean waiting time was under 1 minute irrespective of therapy.[5]

When the maximum waiting time is observed for each recording as opposed to each episode, this again dramatically increased with the selected threshold, and could be several minutes when the threshold set at 600ms.however this maximum is reduced by almost an order of magnitude with digoxin therapy.[5]

Therefore, for patient with sustained rapid ventricular rates during AF episodes, delay may occur before an atrial defibrillation can safely deliver therapy. However, the longest such delays can be greatly reduced with digoxin, such that even with threshold RR interval of 600ms, most patient could be treated by such a device within 10 minutes.[5]

***Effects of dofetilide***

Dofetilide is a new 'pure' class III antiarrhythmic drug that increases repolarization time by blocking the rapid component of the delayed rectifier Ik of the potassium current. Small scale studies on the effect of dofetilide on QT dispersion in normal subject and in patient with stable angina pectoris have shown significant changes. However such lack of changes may be the sum of a decrease in QT dispersion in patient at increased risk from drug induced proarrhythmia and death.[12]

Baseline characteristic for placebo and dofetilide treated patient shown in table 4.baseline QT dispersion was greater in the dofetilide group. Patient with ischemic heart diseases had greater QT dispersion [74(35/156) ms than patient without ischemic heart disease 66(34/129) ms].presence or absence of bundle branch block (BBB) did not influence the QT dispersion: 70 (38/130) ms vs. 74(34/157) ms

**Table-4: baseline characteristic [12]**

| characteristic | Placebo | dofetilide |
|---|---|---|

Study shows a reduction in QT dispersion in 39 patients treated with sotalol compared to placebo treated patients. Another study compared changes in QT dispersion in 38 patients receiving chronic amiodarone treatment secondary to quinidine treatment for ventricular tachyarrhythmia or atrial fibrillation. Nine of these patients had developed torsade de pointes ventricular tachyarrhythmia on quinidine treatment. In all patient maximum QT intervals was prolonged, but for both drug regimes, only the nine patients with an episode of torsade de pointes ventricular tachyarrhythmia on treatment had increased QT dispersion compared to baseline QT dispersion. For the rest of the patients, on treatment had increased QT dispersion was unchanged from baseline QT dispersion. QT dispersion changes to the probability of inducing sustained ventricular tachycardia or ventricular fibrillation in 72 patients with coronary heart disease and baseline inducible sustained ventricular tachycardia or ventricular fibrillation. For both patients with and without on-treatment

Inducible arrhythmias, on-treatment maximum QT interval were prolonged. An increase in QT dispersion was only seen in the treatment failure group.[12]

It is not obvious why changes in QT dispersion induced by dofetilide do not predict mortality. Perhaps the initial assumption that the beneficial effect of class III antiarrhythmic drugs lies in making spatial ventricular repolarization

homogenous is wrong. However, if this assumption is true one has to look for reasons why QT dispersion does not reflect these repolarization changes. Recent studies indicate that QT dispersion is merely an incomplete marker of T wave morphology rather than of repolarization itself. Being both a crude as well as an indirect marker of ventricular repolarization in combination with a low reproducibility could explain the many contradictory studies made on this parameter. Also, QT dispersion is dependent on how QT intervals are measured, and the fact that there is no consensus on how to measure if the QT interval is reflected in the different ways QT dispersion is measured.[12]

## Discussion

Sotalol is used to treat primarily atrial fibrillation, however rarely can be used for the treatment of ventricular tachycardia or ventricular fibrillation. Sotalol can prolong the QT interval.[4] It is recommended that sotalol be initiated in the patient setting in a majority of cases in order to monitor the QT interval after each dose to prevent polymorphic ventricular tachycardia. The National Library of Medicine *(USA)* suggests that atenolol can significantly reduce the risk of myocardial ischemia [4]. The study conducted at the Department of Anesthesia at the University of California, USA suggests that atenolol is able to reduce the risk of death for as long as 2 years after cardio-related surgery. Amiodarone and Lidocaine is used to expand the blood vessel and decreases resistance by lowering levels of angiotensin II. Allows blood to flow more easily and makes the heart's work easier.[cardiac medication, AHA] digoxin increases the force of the heart's contraction, which can be beneficial in heart failure and for irregular heartbeats. .[cardiac medication, AHA]

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