Introduction

The surface electrocardiogram (ECG) records the electrophysiological process where the electric impulses are generated and conducted through the heart muscle tissue. Whereas the P wave represents the electrophysiological action potential of the atria, the QRS complex reflects the ventricular action potential (which masks atrial repolarization), and the T wave corresponds to ventricular repolarization. In turn, the QT interval, which extends from the start of the Q wave to the end of the T wave, represents the time taken for ventricular action potential; depolarization plus repolarization. The QT interval usually has a normal duration of between 200-300ms. For upper normal limit, it must be less than 440 ms in males and 460 ms in females, otherwise the QT interval is prolonged **(Wagner et al., 2007)**.

One important potential cause of ventricular arrhythmia is prolongation of ventricular repolarization presented by prolongation of the QT interval. Prolongation of ventricular repolarization may result in early after-depolarization (EAD), which in turn may induce re-entry and thereby provoke torsade de pointes (Tdp) and fatal ventricular arrhythmia. Sudden cardiac death is among the most common causes of mortality, accounting for

approximately 50% of all deaths from cardiovascular causes and 20% of total mortality. The majority (80% to 85%) of sudden cardiac deaths are caused by acute ventricular arrhythmias **(Bruno et al., 2010)**.

QT interval prolongation was first reported by **Selzer and Wray (1964)** as a response to quinidine. It may be congenital or acquired. Acquired QT prolongation is more prevalent than the congenital form. Several risk factors have been identified with QT prolongation, with QT prolonging drugs as the most frequent cause **(Kallergis et al., 2012)**. Certain drugs reported to prolong QT interval such as antiarrhythmics, antimicrobials, antihistamines, anti-depressants, antipsychotics, anticonvulsants, anesthetics, antianginal, antihypertensives, anticancer agents, antilipemics, diuretics, certain GIT stimulants and antimigraine agents **(Gowda et al., 2004)**.

Other than drugs, many factors for prolongation of the QT interval include female gender, myocardial infarction, dilated cardiomyopathy, congestive heart failure, hypertrophic cardiomyopathy, hypertension, left ventricular hypertrophy, bradycardia, heart block, myocarditis, diabetes mellitus, obesity, anorexia nervosa, liquid protein diet, electrolyte disturbances, hepatic impairment, intracranial hemorrhage and hypothyroidism **(Camm et al., 2004)**.

The main aim of the management of LQTS is to prevent sudden death. A secondary aim is to assist the family in their adjustments that have to be made through time and skilled psychological and genetic counseling **(Skinneret al., 2011)**. Currently, LQTS therapy targets two main distinct strategies: (1) reduction in sympathetic or adrenergic tone by the use of ß-blockers and/or Left Cardiac Sympathetic Denervation (LCSD); (2) correction or cessation of life-threatening arrhythmias via the timely delivery of electrical impulses by an ICD **(Giudicessi et al., 2013)**. Over more, the treatment of LQTS should start with prevention (**Booker et al., 2003**).

Pathogenesis of Acquired long QT syndrome

Cardiac Action Potential

In order to correctly understand the pathophysiology of acquired LQTS, a brief remind of the cardiac action potential is indicated. The cardiac action potential is generated by the changing transmembrane permeability to ion currents such as Na^+, Ca^{2+} and K^+. Like all living cells, the potential inside a myocyte cell is negative compared to the outside (resting transmembrane potential of -80 to -90mV). However, cardiac cells are excitable and when appropriately stimulated, the ion channels within the cell membrane open and close sequentially. This changes the transmembrane ion permeability and leads to the sequential development of the transmembrane potential that is called the action potential **(Camm et al., 2004)**.

The action potential is physiologically divided into 5 phases (0, 1, 2, 3 and 4) as shown in figure 1. The initial depolarization (phase 0) is triggered by the rapid inward sodium (I_{Na}) and the L- and T-type calcium currents ($I_{Ca\text{-}L}$ and $I_{Ca\text{-}T}$), which change the cell potential from -90mV to

30mV. The transient outward I_{to} potassium current is responsible for the slight repolarization immediately after the overshoot (phase 1). During the following plateau phase (phase 2), the cell potential is maintained by a balance between the inward L-type calcium current (I_{Ca-L}) and the electrogenic sodium–calcium exchange current (I_{Na-Ca}), and the outward I_{to} current. The repolarization phase (phase 3) of the myocyte is driven predominantly by outward movement of potassium ions, carried as the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier potassium current. The diastolic depolarization (phase 4) results from a combination of the decay of the outward delayed rectifier I_{Kr} and I_{Ks} currents, which maintains the resting potential at approximately -90 mV, and the activation of the inward pacemaker current (I_f) and the inward sodium background leak current (I_{Na-B}). A variety of other different potassium channel subtypes are also present in the heart. Pharmacological blocking and opening of each of these channels has a different effect on the action potential **(Fermini et al., 2003)**.

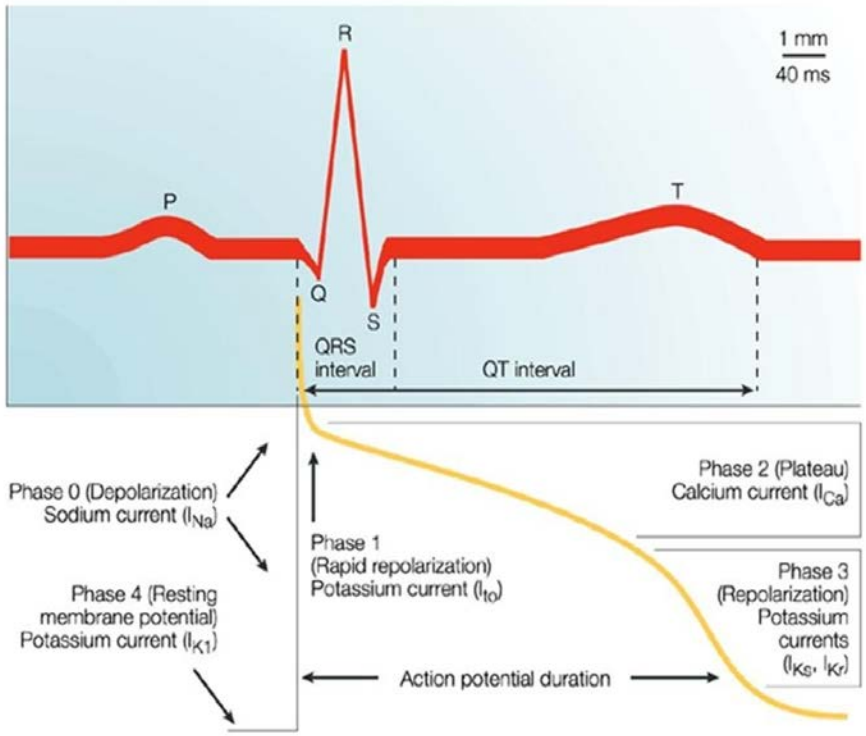

Figure (1): Temporal correlation between action potential duration and the QT interval on the surface ECG. From **Fermini et al., (2003)**.

Determination of the QT Interval

The surface electrocardiogram (ECG) records the electrophysiological process whereby the electric impulses are generated and conducted through the heart muscle tissue. Whereas the P wave represents the electrophysiological action potential of the atria, the QRS complex reflects the ventricular action potential (which masks atrial repolarization), and the T wave corresponds to ventricular repolarization. In turn, the QT interval reflects the duration of

the action potential plus the time associated with electric impulse transmission through the ventricles. The interval between the start of the QRS complex and the end of the T line in turn defines the length of the QT interval (**Wagner et al., 2007)**. (Fig.2)

For determination of the QT interval it is preferable to record the surface ECG at a speed of 50 mm/s and with amplitude of 0.5mV/s, using a multichannel system capable of simultaneously recording all 12 leads. To measure the QT interval, a line is traced tangential to the zone of greatest slope of the descending portion of the T wave. The intersection point between this tangent and the isoelectric line defines the end of the T wave. The small physiological U waves should not be included in measurement of the QT interval. It is preferable to determine the interval from the second axial lead (II), because on this lead the repolarization vectors tend to give rise to a single wave instead of a T wave and a U wave. Nevertheless, the U waves that are not separated from the T waves are considered to be pathological, and can be included in the QT interval **(Abriel et al., 2004)**.

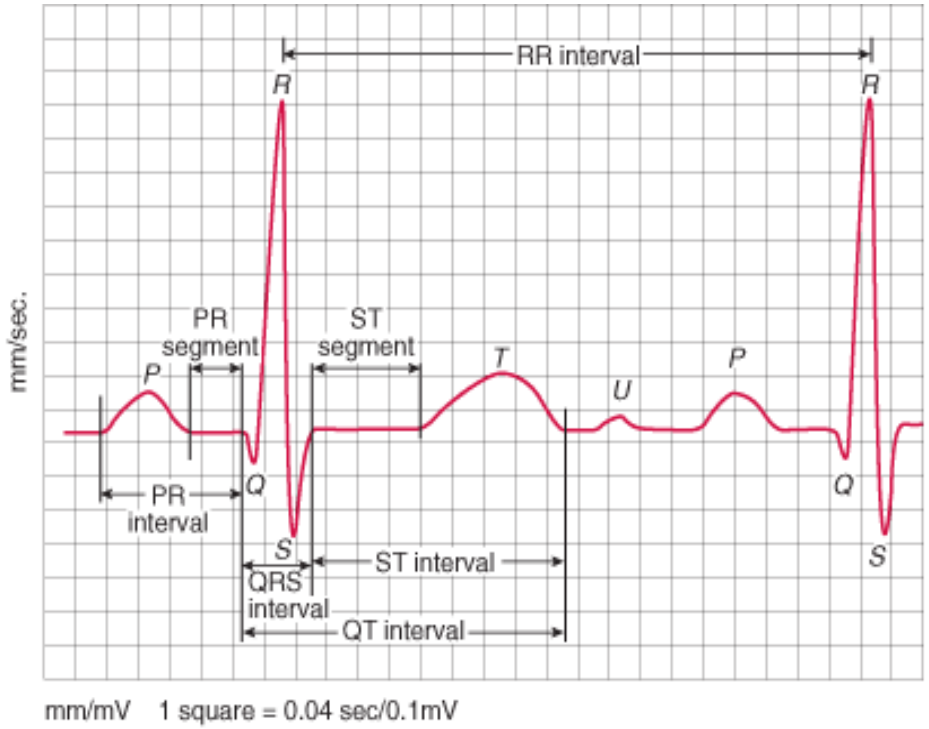

Figure (2): The QT interval. It is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular action potential (depolarization plus repolarization). It is inversely proportionate to heart rate. From **Wagner et al., (2007**).

The QT interval is influenced by heart rate. Therefore, 3-4 RR intervals are measured before the QT interval to correct for frequency. Several possible correction formulas are applied to measure the corrected QT interval (QTc). The most widely used formulas are those of Bazett; QTc = QT/RR1/2 and Fridericia; QTc = QT/RR1/3. The former is more popular, though the latter is more exact for extreme heart rate values. RR is expressed in seconds, as a result of

which in both cases, when RR = 1, i.e., the heart rate is 60 beats per minute (bpm), the QTc = QT. Normal values of the QT interval, corrected to age and sex, are shown in table1. The QT interval usually has duration of between 200-300ms. It must be less than 440 ms in males and 460 ms in females, otherwise, the QT interval is prolonged (Fig. 3) **(Lourdes et al., 2012)**.

Table (1): Suggested Bazett-Corrected QTc Values for Diagnosing QT Prolongation.

	Normal	**Limiting**	**Prolonged**
Adult males	< 430	430-450	>450
Adult	< 450	450-470	>470
Children	< 440	440-460	>460

From **Goldenberg et al., (2006)**.

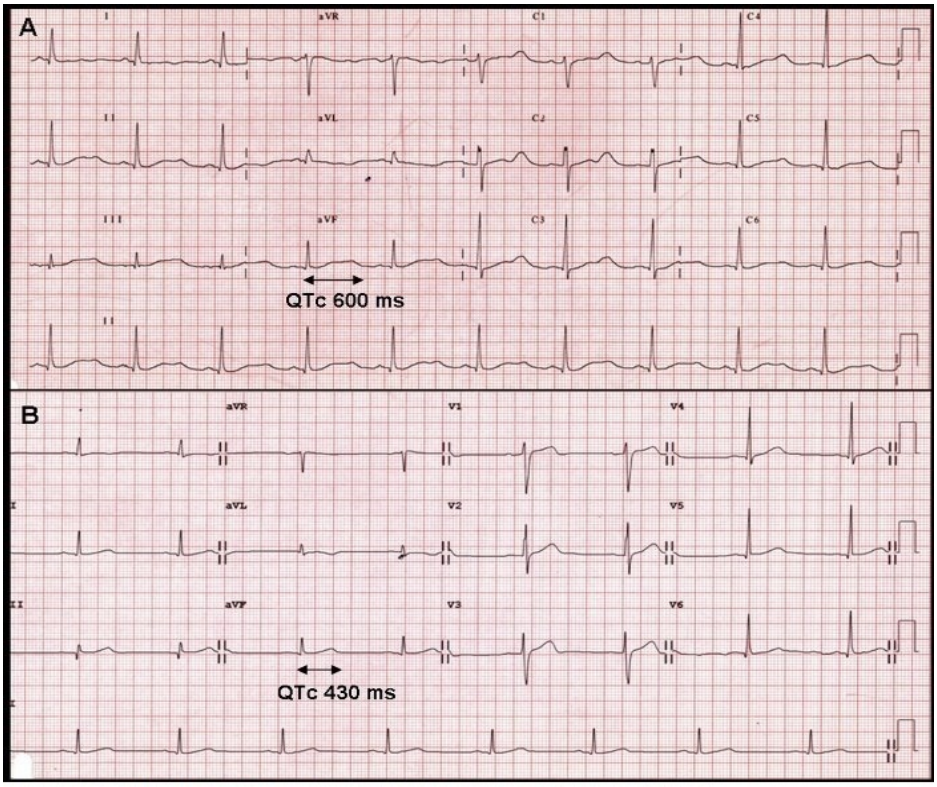

Figure (3): Normal and prolonged QT intervals. From **Lourdes et al., (2012)**.

Definition of Long QT Syndrome (LQTS)

The QT interval represents the duration of the action potential (activation, depolarization and recovery, repolarization) of the ventricular myocardium. Prolonged recovery (delayed repolarization) from electrical excitation increases the likelihood of dispersing refractoriness, when some parts of myocardium might be refractory to subsequent depolarization. From a physiologic standpoint, dispersion

occurs with repolarization between 3 layers of the heart, and the repolarization phase tends to be prolonged in the mid myocardium. This is why the T wave is normally wide and the interval from T_{peak} to T_{end} (T_{p-e}) represents the transmural dispersion of repolarization (TDR). In LQTS, TDR increases and creates a functional substrate for transmural re-entry. LQTS is a disorder affecting myocardial repolarization characterized by a prolongation of the QT interval on electrocardiograms beyond the normal limits, with a propensity to ventricular tachyarrhythmias which may lead to syncope, cardiac arrest, or sudden death. LQTS can be congenital or acquired. The acquired form of LQTS is more common than the congenital form **(Charles et al., 2007)**.

Prevalence of Congenital and Acquired LQTS

The occurrence of long QT syndrome internationally is similar to that in the United States. Regarding the United States, long QT syndrome (LQTS) remains an underdiagnosed disorder, especially because at least 10-15% of LQTS gene carriers have a normal QTc duration. The prevalence of LQTS is difficult to estimate. However, given the currently increasing frequency of diagnosis, the estimated prevalence is around 1: 10.000 individuals **(Murphy et al., 2008)**.

Patients with LQTS usually present with cardiac events (e.g., syncope, aborted cardiac arrest, sudden death) in childhood, adolescence, or early adulthood. However, LQTS has been identified in adults as late as in the fifth decade of life. The risk of death from LQTS is higher in boys than in girls younger than 10 years; the risk is similar in male and female patients thereafter. Furthermore, the QT interval also varies according to patient gender, being longer in women, probably because their cardiac cells generate lesser repolarization currents **(Drici et al., 1996)**.

Newly diagnosed cases of LQTS are more prevalent in female patients (60-70% of cases) than in male patients. The female predominance may be related to the relatively prolonged QTc in women compared with men and to a relatively higher mortality rate in young men. In women, pregnancy is not associated with an increased incidence of cardiac events, whereas the postpartum period is associated with a substantially increased risk of cardiac events, especially in the subset of patients with LQT2. Cardiac events have been highly correlated with menses. Also, a significantly higher risk of cardiac events (a 3-fold to 8-fold increase, mainly in the form of recurrent episodes of syncope) has been reported in women with LQT2 syndrome

during and after the onset of menopause, compared with the reproductive years **(Buber et al., 2011)**.

Mechanism of LQTS

From the historical perspective, as early as **1856, Meissner et al.**, described the case of a deaf girl who suffered a collapse and died after being punished in school. The girl had two siblings that also died after an episode of fear for one and an episode of anger for the other. In **1957,Jerwell and Lange-Nielsen** described the electro-cardiographical principles of the long QT disorder, in a description of four deaf children (three of whom died prematurely) and who presented with a prolongation of the QT interval. Later, other congenital cases without deafness began to be reported **(Romano et al., 1965)**, yielding a total of ten familial long QT syndromes. Conclusively, congenital long QT syndrome is a rare inherited genetic cardiac disorder associated with a prolonged QT interval on surface ECG, recurrent syncope and sometimes a predisposition to sudden death from life-threatening cardiac arrhythmias, including torsade de pointes and ventricular fibrillation **(Yanzong et al., 2010)**.

Although mutations in 12 genes have been identified in approximately 60-70% of the individuals affected with hereditary LQTS, the etiology remains unknown in about one

third of cases **(Zareba et al., 2008)**. These genes include the genes encoding for ion channels (potassium, sodium and calcium) and their associated proteins, resulting in abnormal ion channel kinetics **(Yanzong et al., 2010)**. Based on such genetic background, 10 types of Romano-Ward syndrome (LQTS1-10), 2 types of Jervell and Lang-Nielsen (JLN) syndrome (JLN1-2), 1 type of Andersen syndrome and 1 type of Timothy syndrome are characterized (Table 2) **(Medeiros-Domingo et al., 2007)**.

Three potassium currents (IK1, IKs, and IKr) are believed to be responsible for the majority of ventricular repolarization **(Nerbonne et al., 2005)**. Shortened opening of the potassium channel in LQTS1, LQTS2, LQTS5, LQTS6, JLN1, and JLN2 and delayed closing of a sodium channel in LQTS3 overcharge a myocardial cell with positive ions. The LQT2 gene KCNH2, located on the long (q) arm of chromosome 7, encodes the pore-forming subunit of the potassium channel. The KCNH2 mutation results in diminution of the repolarizing rectifying potassium current (IKr) with abnormal ventricular repolarization.Over 200 mutations in the KCNH2 gene have been identified **(Murphy et al., 2008)**.

Table (2): Genes involved in the long QT syndrome.

LQTS Type	Locus	Mutated Gene	Ion Current Affected
LQT1	11p15.5	KVLQT1 or KCNQ1	Potassium (I_{Ks})
LQT2	7q35-36	HERG, KCNH2	Potassium (I_{Kr})
LQT3	3p21-24	SCN5A	Sodium (I_{Na})
LQT4	4q25-27	ANK2, ANKB	Sodium, potassium, calcium
LQT5	21q22.1-22.2	KCNE1	Potassium (I_{Ks})
LQT6	21q22.1-22.2	MiRP1, KNCE2	Potassium (I_{Kr})
LQT7	17q23.1-q24.2	KCNJ2	Potassium (I_{K1})
LQT8	12q13.3	CACNA1C	Calcium ($I_{Ca\text{-}Lalpha}$)
LQT9	3p25.3	CAV3	Sodium (I_{Na})
LQT10	11q23.3	SCN4B	Sodium (I_{Na})
LQT11	7q21-q22	AKAP9	Potassium (I_{Ks})
LQT12		SNTAI	Sodium (I_{Na})
JLN1	11p15.5	KVLQT1 or KCNQ1	Potassium (I_{Ks})
JLN2	21q22.1-22.2	KCNE1	Potassium (I_{ks})

From **Medeiros-Domingo et al., (2007)**.

LQTS 1-3 account for 95% of known mutations, with different genetic and clinical characteristics for each syndrome. Clinical presentation of congenital LQTS can vary significantly due to the different genotypes and variable penetrance. Affected families tend to have their own novel or ‘‘private’’ mutations. Transmission is not strictly Mendelian with an excess of female carriers among the offspring of mutation carriers **(Murphy et al., 2008)**.