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Prevalence of and Predictors for QT interval Prolongation and Adverse Outcomes in an Acutely Ill Cohort: The QTIP Study.

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Prevalence of and Predictors for QT Interval Prolongation and Adverse Outcomes in an Acutely Ill Cohort: The QTIP Study.

by

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DISSERTATION

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Prevalence of and Predictors for QT Interval Prolongation and Adverse Outcomes in an Acutely Ill Cohort: The QTIP Study.

David Pickham

ABSTRACT

QT interval prolongation on the electrocardiogram is a marker of abnormal ventricular repolarization and is associated with Torsades de Pointes, sudden death, and all-cause mortality in outpatient samples. This is the first inpatient study of acutely ill adults performed to determine the: 1) need for QT monitoring as outlined in American Heart Association (AHA) guidelines, 2) prevalence and predictors of QT prolongation, 3) association of QT prolongation with hospital length of stay and all-cause mortality and 4) ability of acute care nurses to perform accurate QT measurement by routine manual methods. **Methods:** Special study software (Philips Healthcare, Andover, MA) was installed to measure the QT and heart-rate-corrected QT (QTc) interval every minute in all patients admitted to 5 hospital units over a 2-month period. Patient data were abstracted directly from the medical record. Nurses' knowledge and skills were assessed by pre-post tests conducted during QT-related classes repeated 44 times on all nursing shifts. Nurses were taught how to measure the QT interval from a rhythm strip using hand-held calipers and to calculate the QTc using the Bazett formula. **Results**: **Patients**. 67,648 hours of QT data were obtained from 1039 patients. 73% of patients had at least 1 AHA indication for QT monitoring. 24% had an episode of dangerous QT interval prolongation > 500 milliseconds lasting 15 minutes or more. In a multivariate logistic regression analysis, predictors of QT prolongation were female sex, number of proarrhythmic drugs, low potassium or calcium, high glucose or creatinine, and history of stroke or hypothyroidism. An episode of QT prolongation was associated with longer length of stay (11.53 v 5.52 days, p <.0005) and greater all-cause mortality (8.7% v 2.6%, *Fishers exact* p < .0005). Patients with QT prolongation had 3 times the odds for all-cause mortality than those without (OR 2.99; 95% C.I., 1.1 – 8.1). **Nurses**. 391 participated in the classes (81.5% response rate). Education improved nurses' QT knowledge scores (44% v 77%, p <.0005). Nurses ability to calculate the QTc interval also improved (5.6% v 51.9%, p <.0005). **Conclusion.** A majority (73%) of acutely ill patients need QT monitoring and a significant proportion (24%) develop dangerous QT prolongation. QT prolongation is associated with longer hospitalization and 3 times the odds for mortality. With education, nurses' ability to perform QT measurement improves; however, an unacceptably high proportion (48%) is still unable to correctly measure the QTc interval. These data suggest that the need for QT monitoring is high and that software added to hospital cardiac monitors may be valuable to identify high risk patients who may warrant closer follow-up.

Dedications

I would like to dedicate this dissertation to a number of people. First and foremost to my mum Jugsy (Ann), you have done everything a kid could ask of his mum. To my brothers and sisters, if you ever actually stumble across this dissertation and read it, I'll give you a dollar. To my mates at home, you contributed nothing to this dissertation, which is probably the reason why I have actually been able to finish it. To my Mount Sinai friends, thanks. To those family and friends that have passed, I know you've been watching. Grandpa and Grandma I dedicate this to you. Caylee you are too young to know, but one day if you read this, know that you were sitting on my lap with a poke-a-dot onesy sucking your fist and mumbling to the computer while I type this. I want to cherish every moment, you're the best. To the in-laws, I know you wish Dee aimed a little higher, sorry. Thanks for all your support. And of course to Dee, a big thanks for putting up with me.

Finally, this dissertation represents nearly 4 years of work and dedication. To all the patients and families who have been affected by LQTS, I dedicate this work to you. I hope my work adds to our understanding of this disease and takes us a little step closer to a cure.

Acknowledgements

They say it takes a village to raise a child. Similarly, it takes a collaborative team to raise a researcher. With this in mind, I would like to acknowledge the work of many people who constitute ‘my village’.

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CHAPTER 1

STATEMENT OF THE PROBLEM

The QT interval measurement obtained from an electrocardiogram represents ventricular repolarization of the heart. In the presence of noxious stimuli the duration of ventricular repolarization can become abnormal, causing prolongation of the QT interval. This can result in acquired long QT syndrome (ALQTS). ALQTS makes the heart susceptible to developing the arrhythmia Torsades de Pointes (TdP). As secondary prevention for TdP in hospital settings the American Heart Association (AHA) released practice standards recommending that clinicians perform QT interval monitoring for 'at risk' patients (Drew et al., 2004). Monitoring for the development of QT interval prolongation will result in the early identification and intervention, preventing the occurrence of TdP.

ALQTS is most commonly caused by proarrhythmic drugs. In the hospital setting nurses are the primary clinicians administering these drugs. Also, nurses are the sole providers of continuous cardiac monitoring. Therefore, nurses are ideally situated to implement surveillance for, and prevent the occurrence of, ALQTS and TdP. The ability of nurses to perform QT interval monitoring though is currently unknown.

Studies evaluating clinicians' QT interval monitoring skills have primarily focused on physician samples. Initial evidence reveals that as a group, physicians do not adequately possess the skills necessary to accurately and reliably measure the QT interval (Viskin et al., 2005). This is a concern. If clinicians are unable to perform QT interval

monitoring accurately, then the AHA recommendations, assuming they are valid, will not be effective in improving the identification and prevention of ALQTS and TdP.

Currently, the need for QT interval monitoring in a hospital unit providing continuous cardiac monitoring is not known. Establishing the need for QT interval monitoring will directly guide clinical practice, as it will help determine whether it is imperative that *all* clinicians become proficient in QT interval monitoring, or just selected groups, i.e. cardiologists. If the need for QT interval monitoring in patients admitted to a cardiac monitoring unit is low, it may be possible in a team environment to delegate QT interval monitoring to a single staff member who has proven competence with this skill. Alternatively, if the prevalence need for QT interval monitoring is high, then it would be unworkable to delegate this task to one staff member. In this scenario, all clinicians providing care to critically ill patients need to be proficient at QT interval monitoring.

An important aspect in establishing the need for QT interval monitoring, is to establish an evidence based criteria for those who are deemed to be 'at risk' for developing ALQTS and TdP. A paucity of research has been conducted evaluating QT interval prolongation in critical care patients. As a consensus statement, recommendations within the AHA practice standards are based on sample studies, anecdotal case-reports, and basic research findings. Establishing evidence to either support or refute these recommendations is an important first step in evaluating the usefulness of QT interval monitoring in the hospital setting.

Purpose of the Study

The purpose of this study is two-fold. First, we aim to evaluate whether a 1 hour QT interval-intensive education intervention is effective in improving nurses' knowledge and abilities related to QT interval monitoring. Second, this investigation aims to determine the need for QT interval monitoring, the patients most at risk for QT interval prolongation, and whether QT interval prolongation is associated with adverse in-hospital events.

The specific hypotheses of this study are:

1. QT interval-intensive education improves nurses' skills and abilities in performing QT interval monitoring.
2. The majority of patients admitted to a critical care unit have at least one indication for QT interval monitoring.
3. The AHA indications for QT interval monitoring are effective in identifying patients that are at risk for developing QT interval prolongation while admitted to a unit providing continuous cardiac monitoring.
4. Patients' demographic, medical, and clinical data can be used to predict the likelihood of developing QT interval prolongation while admitted to a unit providing continuous cardiac monitoring.
5. QT interval prolongation is associated with increased a) all-cause in-hospital mortality, b) hospitalization and cardiac monitoring time, c) critical intervention (code blue, medical rapid response), and d) device intervention (pacemaker, internal cardiac defibrillator).

Definitions

-The QT interval is a marker for ventricular repolarization. As the duration of the QT interval is largely dependent upon the speed of the cardiac cycle, a correction formula needs to be applied to aid interpretation. This correction results in a QTc interval. Throughout this thesis references are made to both QT interval monitoring and QT interval prolongation. For the purpose of this thesis, these terms are considered to be synonymous to QTc interval monitoring and QTc interval prolongation.

-QT interval monitoring data within this thesis was obtained from a continuous QT interval monitoring software installed in the Philips Intellivue Patient Monitoring System. This system provides a QT interval measurement by forming representative waveforms for each lead, median beat selection, and measurement from root-mean-squared (RMS) waves. As such, this measurement is referred to within this thesis as the *mean QT interval*. The mean QT interval is provided per minute for the patient's length of stay. To ascertain the patients mean mean-QT interval duration, the mean QT interval was averaged over time. This was then termed the averaged-mean QT interval for the purpose of this thesis.

Introduction to the Problem:
History, Significance, and Sub problems.

Historical Review

Understanding Long QT Syndrome (LQTS) requires an understanding of the separate yet parallel developments of both acquired LQTS and congenital (*C*-) LQTS. Initially clinicians treated these diseases as separate entities and to an extent, especially with CLQTS in the young, this persists. However it is becoming increasing clear that LQTS in adults is a multifactorial disease caused by acquired and congenital factors. It is important to note that as a syndrome QT interval prolongation needs to persist in the presence of other associated factors, e.g. syncope or sudden cardiac death. QT interval prolongation alone does not warrant a diagnosis of LQTS.

Romano and Ward (1964) as well as Jervell and Lange-Nielsen (1957) separately described two syndromes that consisted of baseline QT interval prolongation within related family members. These seminal works led to the identification of the first two CLQTS syndromes: 1) the Romano-Ward Syndrome and 2) Jervell-Lange-Nielsen Syndrome. The first gene responsible for causing CLQTS was identified by Mark Keating and colleagues at the University of Utah (1995). Since then 11 further genes have been identified and hundreds more mutations.

ALQTS was first described in the literature around the same time as CLQTS. Unlike CLQTS though, individuals with ALQTS experience transient prolongation of the QT interval. The duration of an ALQTS episode is thought to be abbreviated only by the removal of the offending stimuli (Kannankeril & Roden, 2007). A classic example of one of the earliest known agents to cause ALQTS is quinidine.

Quinidine is a well known class 1a anti-arrhythmic that decreases cardiac conduction and prolongs repolarization time by slowing sodium and potassium ion exchange across the cardiac cell membrane. It was commonly used in the management of atrial and ventricular tachyarrhythmias (Bryant, Knights, & Salerno, 2003), though has fallen out of vogue due to its potential deleterious side effects. Syncope, a well known side effect of quinidine administration, has been described as being something 'sudden, seldom preceded by warning prodromes, and consisted of immediate loss of consciousness, cessation of respiration, and involuntary muscular contraction' (Selzer & Wray, 1964). An early study by Thompson (1956) of 611 subjects administered quinidine, revealed that 20 patients died due to something that was "not susceptible to pathological explanation". Shortly thereafter, Selzer and Wray (1964) explained this phenomenon, attributing quinidine syncope to the cardiac arrhythmia "Paroxysmal Ventricular Fibrillation". Two years later a French physician named Francois Dessertenne (1966) coined the term that remains in use today, Torsades de Pointes.

Since then, the science behind ALQTS progressed very little. It was not until The Cardiac Arrhythmia Suppression Trial (CAST) findings were released in 1989 that clinicians, researchers and regulators began to evaluate the risks associated with ALQTS. The CAST aimed to "evaluate the efficacy and safety of arrhythmia suppression therapy in patients with asymptomatic or mildly symptomatic ventricular arrhythmia after myocardial infarction" (The Cardiac Arrhythmia Suppression Trial (CAST) Investigators, 1989). Enrollment began in 1987 and within a year the study's Data and Safety Monitoring Board (DSMB) discontinued two of the treatment arms (flecainide & encainide) due to increased total mortality and sudden arrhythmic death. A second CAST

study was begun with moricizine as the sole treatment group. Like the first CAST, the second CAST (CAST II) was stopped early due to excessive mortality and non-fatal cardiac arrests in the drug treatment group (CAST Investigators, 1989; CAST II Investigators, 1992). Overall, the CAST studies demonstrated that commonly administered drugs have potentially deadly side effects. The repercussions of these studies continue to be felt today.

After the results of the CAST studies were published, regulators began to examine the safety of other drugs. Through analyzing post-market surveillance data, as well as clinical and pharmacologic data, many drugs were determined to possess potentially proarrhythmic effects. Consequently, droperidol (United Kingdom only), terfenadine, levacetylmethadol, sertindole, astemizole, grepafloxacin, terodiline, lidoflazine, prenylamine, cisapride and more recently in 2005, thioridazine was withdrawn from clinical use. Other drugs such as pimozide, halofantrine, ziprasidone, moxifloxacin, and gatifloxacin had restrictions placed on their prescribing, while others, like haloperidol have had black box warnings (I.e., a warning statement from the Food and Drug Administration [FDA] regarding serious side effects) added to their product labeling.

With the growing awareness of ALQTS, the European Medicines Evaluation Agency's Committee for Proprietary Medicinal Products (CPMP) in 1996 established a working group to provide drug safety guidance to the pharmaceutical industry. In 2002 HealthCanada followed closely by the FDA, produced similar regulatory guidelines. By May 2005, The International Committee on Harmonization (ICH) (2005) released an over-arching document standardizing drug safety testing for new pharmaceuticals. But many drugs were marketed before these guidelines were published.

Surveillance for post-market drug safety is the responsibility of clinicians. However, unlike pharmaceutical companies with sophisticated monitoring techniques and limitless scientific resources, the clinician is alone and reliant upon his/her own knowledge, skills and judgment to be able to correctly categorize and treat patients developing ALQTS. In 2004, practice guidelines for QT interval monitoring were released by the American Heart Association (Drew et al., 2004). Though overdue, many of the practice recommendations are based on expert consensus (Drew et al., 2004) and have not been validated in the critically ill sample. For clinicians providing evidenced based care, the lack of empirical evidence combined with the QT interval's poor predictive value for TdP has resulted in QT interval monitoring being poorly understood and under-utilized.

Significance of Long QT Syndrome

Sudden cardiac arrest (SCA) kills approximately 325,000 Americans each year (American Heart Association (AHA), 2008). Aptly named, SCA is an abrupt unexpected loss of cardiac electrical activity in individuals with or without preexisting heart disease (AHA, 2008). Once an individual has suffered a SCA the window for survival decreases 7 -10% each minute (AHA, 2003). After 10 minutes without intervention their chance of survival is minimal. Up to 95% of all SCA events end in death (AHA, 2006). The majority of SCA's are attributable to acquired causes: atherosclerosis, high blood pressure, inflammatory conditions, degenerative conditions, and drugs (AHA, 2003).

Congenital Long QT Syndrome

Congenital LQTS affects 1 in 2500 individuals (Ackerman, 2008) and contributes to 3000 - 4000 sudden cardiac deaths each year (Sovari et al., 2009). Genetic testing of patients with an undeterminable cause of death, reveals CLQTS to be the most common cause (Tester & Ackerman, 2007). It is estimated that 6% of those with CLQTS die before the age of 40, many (30%) die during their first syncopal episode (Sovari et al., 2009).

CLQTS is caused predominately by one or more mutations in the deoxyribose nucleic acid (DNA) that encodes critical pore-forming cardiac ion channels. Changes in these protein structures can cause abnormal cardiac repolarization that provides the substrate for the development of arrhythmia, causing syncope, and if not aborted, sudden cardiac death in an otherwise healthy person (Tester & Ackerman, 2008). A silent disease, these endpoints may be the first sign an individual has that they carry a CLQTS mutation (Casini, Wilde, & Tan, 2008, p. 174). Several distinct CLQTS subtypes have been identified.

jervell-lange-nielsen syndrome (JLNS). Jervell-Lange-Nielsen Syndrome is a rare autosomal recessive disease first described by Jervell and Lange-Nielsen (1957). It exhibits abnormal prolonged cardiac repolarization and profound deafness, and is caused by mutation in the KCNQ1 gene responsible for encoding the alpha-subunit of the delayed rectifying voltage-gated potassium channel (I_{Ks}), or the KCNE1 gene, an interacting protein that contributes to the formation of I_{Ks} (Sanguinetti et al., 1996; Wang et al., 1996). Alteration in either of these proteins results in a loss of potassium ion

regulation in cardiac muscle and in the inner ear. Hence, this disease leads to prolonged cardiac repolarization and profound deafness.

timothy syndrome. Timothy Syndrome is an autosomal dominant hereditary syndrome resulting from variation in the CACNA1C gene, responsible for encoding a sub-unit of the L-type voltage-dependant calcium channel ($I_{Ca\text{-}L}$) (Splawski et al., 2004). Although it can cause QT interval prolongation, its designation as a true LQTS is debated, as not all patients with Timothy syndrome have QT interval prolongation. Expressed throughout the body, mutation in this gene results in a multi-system effect including, abnormal prolonged cardiac repolarization, syndactyly (digit webbing), structural heart defects, facial deformities (round face, alopecia), and autism.

andersons-tawil syndrome (ATS). Andersons-Tawil Syndrome is an autosomal dominant syndrome resulting from variation in the KCNJ2 gene encoding the inwardly-rectifying potassium channel (I_{K1}) (Plaster et al., 2001). Similar to Timothy syndrome, whether ATS should be classified as a LQTS is also debated. Expressed throughout skeletal and cardiac muscle, mutation in this gene results in periodic muscle weakness, abnormal prolonged cardiac repolarization, and structural anomalies: low-set ears, small mandible, 5^{th} digit clinodactyly (curving), short stature, and scoliosis.

romano and ward syndrome (RWS). Romano Ward Syndrome is the most common CLQTS. It is autosomally dominant and results in abnormally prolonged cardiac repolarization and syncope. Genetic testing has identified RWS to be associated with multiple genes responsible for different facets of cardiomyocyte functioning; pore-formation of ion channels, I_{Ks} (Wang et al., 1996), rapid rectifying voltage-gated

potassium channel (I_{Kr}) (Curran et al., 1995), I_{K1} (Plaster et al., 2001), and voltage-gated sodium channel (I_{NA}) (Splawski et al., 2002), $I_{Ca\text{-}L}$ (Splawski et al., 2004), and their beta subunits: I_{Ks} (Sanguinetti et al., 1996), I_{Kr} (Abbott et al., 1999), and I_{Na} (Medeiros-Domingo, Kaku et al., 2007). Two recent genes identified in association with this disorder code for the A-kinase anchoring protein, responsible for organization of the sodium-calcium exchanger (Chen et al., 2007), and syntrophin alpha 1, a submembranous protein that forms part of the cardiomyocyte's structural matrix (Wu et al., 2008).

Current testing is able to detect a mutation in up to 70% of individuals with CLQTS (Napolitano et al., 2005). Thus, it is thought that up to 30% of CLQTS mutations remain to be identified.

Acquired Long QT Syndrome

Drugs are a major cause of SCA and are the largest contributors to ALQTS with over 100 therapeutic agents identified to be able to prolong ventricular repolarization (Litwin, Kleiman, & Gussak, 2008, p. 705). In an evaluation of 4.8 million patients, 1.1 million patients had filled over 4.4 million prescriptions for proarrhythmic drugs (Curtis et al., 2003). Nearly 100,000 patients (9.4%) received two or more proarrhythmic drugs. In the outpatient setting nearly one quarter of all individuals are on a proarrhythmic drug (Curtis et al., 2003).

De Ponti et al. (2002) tracked non-cardiac drug data from 7 countries: Australia, Germany, Sweden, Denmark, England, Italy and Greece. By standardizing drug data, and stratifying drugs by their strength of evidence for proarrhythmia, they found that drugs with published reports of TdP had total sales of 12.9 - 29.1 drug doses per 1000 people

per day. Drugs with black box warnings had 5.8 - 15.3 drug doses per 1000 people per day. In a country with over 10 million people, this equates to a lower bound estimate of 129,000 proarrhythmic drug doses sold per day and 58,000 doses of drugs with black box warnings per day. Together these studies demonstrate that proarrhythmic drugs are significantly prescribed and utilized in the community. The effect of these drugs within the community is unknown.

The prevalence of QT interval prolongation varies depending on the sample being studied. For example, in a study of healthy athletes, 80 (0.04%) subjects had a QT interval that was considered prolonged (Basavarajaiah et al., 2007). This was much lower than the National Health and Nutrition Examination Survey (NHNES) of subjects over 40 years of age. They determined that 6.6% of participants had a QT interval that was considered to be prolonged (Benoit, Mendelsohn, Nourjah, Staffa, & Graham, 2005). This was supported by findings from the Framingham Study (5.4%) (Goldberg et al., 1991). In select samples, the prevalence of QT interval prolongation may be much higher.

A study of consecutive patients admitted to a medical unit (n = 258), determined that 25.2% had QT interval prolongation on their initial 12 lead electrocardiogram (Golzari, Dawson, Speroff, & Thomas, 2007). Similarly a study of elderly subjects (n = 76) administered psychiatric medications found a prevalence rate between 21% and 29% (Dumontet, Malyuk, Kiang, & Procyshyn, 2006). Prevalence rates in other samples vary: methadone 30% (Ehret et al., 2006; Fanoe, Hvidt, Ege, & Jensen, 2007), AIDS 45% (Sani & Okeahialam, 2005), and alcoholics 46.8% (Otero-Anton et al., 1997).

The incidence of TdP in those with QT interval prolongation is difficult, if not impossible to estimate for two related reasons. First, the diagnosis of TdP is made by analyzing the electrocardiographic data for the rhythm's initiating sequence in the presence of QT interval prolongation. Without evidence capturing the onset of the arrhythmia, TdP is impossible to diagnose. Second, the onset of TdP is sudden and without warning. In the community, unless already undergoing cardiac monitoring, electrocardiographic evidence cannot be obtained. Instead death is attributed to SCA. Attempts to ascertain the incidence of TdP have been made. Conservative estimates range from 8.6 cases per 10 million people in the community, to 40 cases per 10 million subjects receiving proarrhythmic drugs in the community (Litwin et al., 2008, p. 714). Much higher estimates of 1 in 100,000 to 1 in 10,000 drug exposures have also been suggested (Fenichel et al., 2004). The true incidence of TdP however is unknowable.

During drug development, drug safety trials can be underpowered, exposing only a few thousand healthy subjects to a drug compound. When a drug is marketed and exposed to 10 million people, a proarrhythmic effect of 1 in every 100,000, would lead to 100 deaths. Behind hepatotoxicity, this above scenario is the most common reason for drugs to be withdrawn from clinical use (Frueh, 2007). Data from the Netherlands, a sample of over 16 million people, reveals that 320 people died as a result of SCA attributable to administration of a non-cardiac drug (Litwin et al., 2008, p. 712). If this were extrapolated to the United States with a sample of over 300 million, this would equate to approximately 6000 deaths (Litwin et al., 2008, p. 712). Post-market surveillance however is unreliable. Current estimates reveal that only 1 out of every 10

drug-related adverse events are reported (Darpo, 2001). As such the impact of proarrhythmic drugs on the community remains unknown.

Confounders Limiting In-Hospital QT interval Monitoring

Monitoring drugs for their potential proarrhythmic effect in the community is difficult. One study estimates that nearly 1/4 of all subjects reviewed (N = 4,400,000) filled at least 1 prescription for a proarrhythmic drug (Curtis et al., 2003). Providing regular QT interval monitoring to these patients would place a tremendous burden on clinicians and cripple the primary health care system. In a hospital setting however, the centralization of resources makes monitoring the QT interval of patients receiving proarrhythmic drugs feasible.

Ability of Clinicians

The successful adoption of the AHA practice standards (Drew et al., 2004) related to QT interval monitoring is largely dependent upon the knowledge and skills of clinicians. Research conducted thus far reveals that the majority of clinicians (physicians) do not possess the knowledge and skills necessary to perform QT interval monitoring reliably (Al-Khatib et al., 2005; Viskin et al., 2005). Arguably nurses are the primary clinicians monitoring for ALQTS, though studies assessing monitoring competency of nurses have not been conducted. Pilot study data suggests that nurses' knowledge and skills of QT interval monitoring is low, but similar to that of general physician samples (Pickham & Drew, 2007). Studies assessing QT interval knowledge that have been conducted thus far are discussed further in Chapter 3.

Method for Measurement

The AHA practice standards recommend measuring the QT interval in patients who are at risk for developing TdP at least once per shift, and before and after administration or adjustment of a proarrhythmic drug. Three distinct methods varying in their reliability and accuracy are currently used in the hospital setting: manual, semi-automated, and automated.

Manual measurement is the most frequently used and least reliable method for monitoring the QT interval. It is entirely dependent upon the clinician's knowledge and skill, and is therefore susceptible to interpretation and measurement errors. The clinician randomly selects the QRST complex that will be used in constructing the QT interval measurement. The RR and QT intervals are measured by hand and the durations calculated with reference to standardized grid markings on electrocardiograph paper. This measure is often rounded to the nearest 40 milliseconds (1 small box) to ease calculation. The QTc interval measurement is calculated by applying the QT interval correction formula to the QT and RR data. Any formula may be used. This method is the most labor intensive and least reliable.

In the semi-automated method, the clinician isolates the rhythm strip of interest at the central monitoring station. Using the computerized system, the clinician is able to slow the paper speed down and improve wave point recognition. Similar to the manual method the clinician measures the QT and RR intervals, though digitally. These are then used to automatically calculate the QT interval. The accuracy of this measurement is bound by the clinician's ability to identify the Q wave onset and T wave offset

accurately. Allowing the clinician to manipulate the cardiac rhythm digitally and automating the QT interval calculation, improves the reliability and accuracy over that of the manual method.

The final method for monitoring the QT interval is the fully automated method. Electrocardiograph companies use proprietary methods to calculate the QT interval. Commonly, these systems superimpose all 12 electrocardiograph leads to determine the earliest Q wave onset and latest T wave offset (Pentti M. Rautaharju, Surawicz, & Gettes, 2009). This is considered to be a better representation of total ventricular repolarization time than single lead methods. However, superimposing rhythms can lead to significant errors. Computers have difficulty determining the Q wave onset and the T wave offset with fast paced rhythms, those with low amplitude T waves, or with significant artifact: competent manual over-read is required (Pentti M. Rautaharju et al., 2009). Additionally, as this method uses the earliest Q wave onset and latest T wave offset, there is little agreement with other measures obtained using single lead methods. Invariably automated measures are longer (Pentti M. Rautaharju et al., 2009). As a result, clinicians are recommended not to use the automated QT interval measurement in the evaluation for LQTS (Ackerman, Khositseth, Tester, & Schwartz, 2008, p. 467). In light of these recommendations, the best method for determining the QT interval measurement remains unclear.

T Waves, U Waves and TU Waves

There is significant inter-reader variability when performing QT interval monitoring (Pentti M. Rautaharju et al., 2009), especially in identifying the T wave

offset. Normal T wave morphology varies between each lead of the electrocardiogram: positive in leads I, II, V_{3-6}, negative in aVR, and varied in aVL, lead III and V_{1-2} (Pentti M. Rautaharju et al., 2009). Clinicians need to be skilled in identifying the T wave offset when presented with varying T wave morphologies (Lanjewar, Pathak, & Lokhandwala, 2004). Especially challenging is the presence of U waves and TU wave complexes.

The origin of TU wave complexes is not entirely understood; three main hypotheses exist. First, the TU wave represents delayed repolarization of the His-Purkinje system (Watanabe, 1975); though researchers question whether the small quantity of cells within the His-Purkinje system could generate the TU wave complexes that are present with LQTS (Antzelevitch & Nesterenki, 2003, p. 119). Second, as mid-myocardial (M) cells possess similar characteristics to Purkinje cells, it is proposed that the TU wave complexes are generated by their late repolarization (Antzelevitch & Sicouri, 1994); this however has not been replicated in laboratory studies (Antzelevitch & Nesterenki, 2003, p. 119). The third hypothesis, and the most supported, is that the TU wave is not a separate U wave, but an interruption of M cells extended action potential, causing a splitting of the T wave; a T2 wave (Yan & Antzelevitch, 1998). Various T wave morphologies are caused by these interruptions with morphology differing depending on the time and magnitude of normal voltage gradient shifts across the myocardium (Antzelevitch, 2006). This third hypothesis is not unanimously supported.

In a commentary, Conrath and Opthof (2005) state that another etiology must be responsible, as there are instances of U waves being separated from T waves by a short iso-electric interval. They go on to state that if the U wave was a T2 caused by late M cell

repolarization, then a return to the iso-electric baseline would not occur. This return to baseline is suggestive of a separate U wave.

Unlike TU wave complexes, U waves are considered 'normal' in young and healthy individuals. They are separate from T waves and become more prominent with slower heart rates (Litwin, Kleiman, & Gussak, 2008, p. 709). Many hypotheses have been suggested to explain their etiology. The theory that U waves are caused by delayed-after-depolarization's resulting from a mechanical stimulus (Antzelevitch & Nesterenki, 2003, p. 121) is gaining the most support among researchers.

The etiology of the T/U wave phenomenon and U waves remains controversial. If the TU wave is actually a T2 wave, then it stands to reason that the entire wave should be included in the QT interval measurement. Additionally, if the U wave is a delayed-after-depolarization then this wave should be excluded in the analysis of the QT interval. For clinicians this distinction is difficult. Uniformity in locating the T wave end point is needed.

QT Interval Correction

There is intense debate regarding how best to account for heart rate's affect on the QT interval. When a patient's heart rate is slow, the duration of ventricular repolarization is long. Alternatively, when a patient's heart rate is fast, the duration of ventricular repolarization is short. An inverse relationship exists. Proposals to adjust for this affect, allowing the QT interval to be interpretable during varying heart rates, was first suggested separately by Bazett (1920) and Fridericia (1920).

However these early correction formulas used non-linear functions to account for fluctuations in the QT interval caused by changes in heart rate. More recently repolarization has been shown to be highly individual. Consequently, any correction formula using a fixed coefficient to adjust for heart rate, without considering the patient's individual repolarization characteristics, risks substantial residual error (Kowey & Malik, 2007). With this in mind, it has since been shown that both Bazett's and Fridericia's correction formulas over-correct in the presence of high heart rates and under-correct in the presence of low heart rates, to varying degrees (Luo, Michler, Johnston, & MacFarlane, 2004; Puddu et al., 1988).

As a result, linear corrections such as the Framingham (Sagie, Larson, Goldberg, Bengtson, & Levy, 1992) and Hodges formulae have been proposed (Hodges, Salerno, & Erlien, 1983). To date, thirty one different non-linear and linear correction formulas have been developed (Malik, 2002), each claiming to 'fit' the RR/QT interval data more precisely. Unfortunately, due to their increasing complexities, these formulae are impractical for use in the clinical setting, and as such have failed to be adopted with any uniformity.

Increasingly, individualized correction formulas are considered to be the best method for adjusting for the affect of heart rate. These are constructed by measuring the subject's QT interval over time and at varying heart rates, under ideal conditions (Gussak & Antzelevitch, 2003; Malik, 2004; Smetana, Batchvarov, Hnatkova, Camm, & Malik, 2003). The impracticality of this in the hospital setting is evident. Determining multiple QT intervals under stress-free conditions is impossible with critical care patients.

The most widely used correction formula in clinical practice is the Bazett's formula. The acceptance of Bazett's correction formula over others is largely due to its comparative ease of use when compared to other non-linear and linear formulae, the lack of sufficient alternative, and the associated error is thought to be small enough not to adversely affect clinical decisions (Malik, 2002; Malik & Camm, 1996). Though recent practice recommendations favor the use of a linear formulae (Pentti, Rautaharju et al., 2009). The confusion regarding their appropriateness has naturally carried over into the clinical setting. Currently, clinicians utilize any correction formula they believe acts best or are most familiar with. A clear standard utilizing a common method is needed.

Frequency of QT Measures

The onset of ALQTS for patients in the hospital setting is variable and difficult to predict. It is caused by both genetic and acquired factors that differ between patients, and within patients, day to day. When ALQTS does occur, its duration is thought to be transient with removal of the noxious stimuli normalizing the QT interval.

Current recommendations advise measuring the QT interval at least once every 8 hours in those at risk for TdP, and before and after each proarrhythmic drug administration (Drew et al., 2004). Though inadequate to capture an event that may be of short duration, it is the first step to introducing QT interval monitoring into clinical practice. To prevent ALQTS and TdP, more frequent QT interval monitoring is required and should be tailored to meet the patient's needs. Presently, nurses are the primary clinicians performing cardiac monitoring, though infrequently, if at all, perform QT interval measurements (Helfenbein et al., 2006). It is possible that a continuous QT

interval monitoring system, as used in this investigation, alleviates the burden frequent monitoring has on nurses and improves identification of episodes of QT interval prolongation. Whether this improves detection and prevention of ALQTS remains to be seen.

Rhythm Disturbance and QT Measurement

Methods for QT interval monitoring require consistent QT/RR intervals. In patients with irregular rhythms, each QT/RR interval relationship differs. Selecting 1 QRST complex would not be representative of overall ventricular repolarization. Recommendations have been made to account for this. One common recommendation is to average as little as 3 (Ackerman et al., 2008, p. 467) or as many as 10 QT interval measures (Al-Khatib, LaPointe, Kramer, & Califf, 2003). This is however labor intensive, and increases substantially the chance for error. Recently clinicians have been recommended not to attempt QT interval correction with rhythms possessing large RR variability (Pentti M. Rautaharju et al., 2009). For bedside nurses this recommendation provides little guidance.

Wide QRS complex rhythms are also challenging for clinicians performing QT interval monitoring. On the electrocardiogram it is impossible to define the exact onset of ventricular repolarization. Therefore the QT interval is a measure of both depolarization and repolarization time. When ventricular depolarization is prolonged it is difficult to ascertain whether the overall increase in QT interval length is due to increases in depolarization time or true prolongation of ventricular repolarization time. The use of the JT interval, a measure from the J point to the offset of the T wave, has been evaluated as

a substitute for the QT interval in patients with wide QRS complex rhythms (Rautaharju, Zhang, Prineas, & Heiss, 2004; Zhou, Wong, Rautaharju, Karnik, & Calhoun, 1992). However, as yet, this method has not been verified as a reliable substitute (Pentti, Rautaharju et al., 2009). Recommendations for determining true ventricular repolarization prolongation in patients with wide QRS complex durations, remain to be determined (Al-Khatib et al., 2003).

Summary

ALQTS results in SCA by providing the substrate for the arrhythmia TdP. The true incidence of TdP and the prevalence of QT interval prolongation and ALQTS are largely unknown. The fact that SCA is a significant cause of mortality makes knowledge of and prevention for these two phenomena, imperative.

ALQTS is predominately caused by administration of a potentially proarrhythmic drug. Secondary prevention for TdP requires monitoring electrocardiographic data for episodes of QT interval prolongation. In the hospital setting, nurses are ideally situated to monitor for and identify cases of QT interval prolongation. Current monitoring though is not ideal. Due to a lack of empirical evidence clearly delineating many facets of QT interval monitoring, confusion and reduced skill acquisition has developed among clinicians. If QT interval prolongation is rarely evident in the acutely ill sample, it is not essential for all clinicians to be competent in this skill.

In this investigation, we undertake the first evaluation of nurses' knowledge and abilities as they relate to QT interval monitoring. Additionally, we aim to determine the need for QT interval monitoring in the critical care setting, the prevalence of QT interval

prolongation in acutely ill patients, variables contributing to predict those developing QT interval prolongation, and the association between QT interval prolongation and adverse in-hospital events. To completely characterize QT interval prolongation in an acutely ill sample, our investigation uses a new continuous QT interval monitoring system (Philips Medical System), providing QT interval data for the patient's entire length of hospitalization.

CHAPTER 2

LITERATURE REVIEW AND CONCEPTUAL FRAMEWORK

Sudden cardiac arrest (SCA) is responsible for the deaths of approximately 325,000 Americans each year (AHA, 2008). Of these deaths, it is estimated that up to 2% are due to ALQTS (Litwin et al., 2008, p. 712) and approximately 1% are due to CLQTS (Ackerman et al., 2008, p. 470). When SCA occurs in patients with LQTS, it is commonly due to the polymorphic ventricular tachycardia, Torsades de Pointes (TdP) (Roden et al., 1996). Torsades de Pointes is an opportunistic arrhythmia requiring an environment with transmural and spatial repolarization differences. This chapter will explore this phenomenon, its contributing factors, and its relationship with LQTS. Basic knowledge of the heart and its normal function is imperative to understanding the cardiac changes underlying TdP, and will therefore be discussed in detail. A review of the literature pertaining to the prevalence of QT interval prolongation and its association with adverse clinical outcomes will conclude this chapter.

Introduction to Cardiac Function

Over the average lifespan, the heart will contract 2.5 billion times; 85,000 times a day. Electrical signaling is the stimulus for normal cardiac function. This signal originates in the sino-atrial (SA) node, a group of specialized pacemaker cells located in the right atrium. The signal is then propagated throughout the heart by a specialized conduction system: SA node through the intra-atrial conduction pathways to the atrio-ventricle (AV) node, through the bundle of his, the left and right bundle branches, and through the ventricles terminating in the Purkinje fibers. As this signal travels throughout

the heart, depolarization of the cell causes mechanical contraction. At the organ level this process appears uniform, though subtle yet important differences exist throughout the heart.

Cardiac Physiology

The heart wall contains three main layers: 1) the endocardium, a smooth endothelial layer, 2) the myocardium, a thick muscular layer, and 3) the epicardium, a protective outer layer of fatty tissue. In the myocardium there are three distinct types of cells (cardiomyocytes) named primarily for their location: 1) endocardial cells, from the sub-endocardium, 2) M-cells, from the mid-myocardium, and 3) epicardial cells, from the subepicardium (Antzelevitch, Zygmunt, & Dumaine, 2003, p. 65). Each type of cardiomyocyte has distinct physical properties that inadvertently contribute to the development of LQTS and TdP.

Structurally, cardiomyocytes are extensively branched throughout the myocardium and are bound together at junctions known as intercalated disks. At these junctions cardiomyocytes are bound, providing a direct, rapid electrical connection between cells; this junction also allows free movement of ions and molecules. Additionally, the contractile unit of the cardiomyocyte (sarcomere) is connected to the cell's membrane (sarcolemma) at this site. Here the sarcomere interacts with other sarcomeres, forming a cohesive structural unit that works in unison to perform cardiac contraction.

Cardiomyocyte's sarcolemma is a lipid bilayer that separates extracellular and intracellular environments. Imbedded within this membrane are selective and non-

selective ion channels, ion pumps, receptors, and protein exchanges, responsible for regulating the flow of ions in and out of the cell (Ackerman & Clapham, 2004, p. 311). These structures, when altered, play a key role in the development of LQTS.

Electrophysiology

Membrane Potential

The sarcolemma maintains differences between the cells internal and external environments. Internally the concentration of potassium (K^+) and chloride (Cl^-) ions are high, while externally sodium (Na^+) and calcium (Ca^{2+}) ion concentrations predominate. Fundamentally, unobstructed ions move from an area of high concentration to an area of low concentration. When ions no longer pass through the semi-permeable membrane, the electrical and chemical forces are balanced (Ackerman & Clapham, 2004, p. 312). This is known as equilibrium and occurs when the heart is at rest. As there are differences in the concentration of charged particles on either side of the sarcolemma, an electrical potential is created. This is known as the *membrane potential* and fluctuates with the movement of ions.

The exact movement of ions across the sarcolemma can be predicated through two equations. The Nernst Equilibrium Potential equation allows researchers to predict the membrane potential when there is a single ion concentration difference, and the more complex Goldman-Hodgkin-Katz equation allows prediction of membrane potential with multiple ions (Katz, 2006, p. 392). Together, ions participating in cardiac function draw the cell membrane towards their respective equilibrium. The resting membrane potential is the net result of these forces and is approximately -90mV.

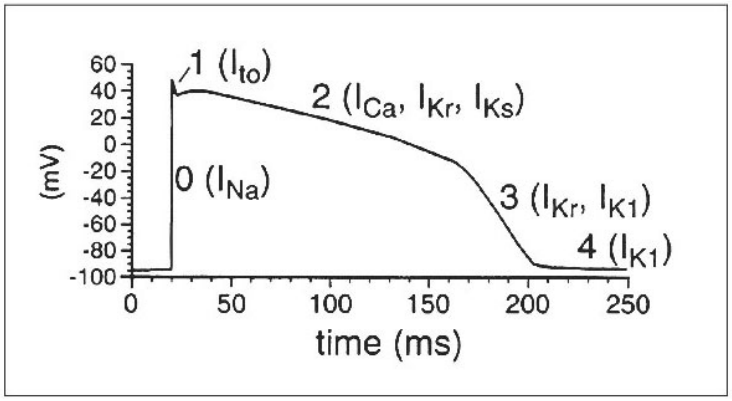
Ventricular Action Potential

The basic functioning of epicardial cells, M cells, and endocardial cells are the same, though there are small important differences in their timing. These differences are an important contributor to the development of ALQTS and TdP. A basic understanding of the typical action potential is needed to conceptualize these differences. The typical ventricular action potential consists of 5 phases.

phase 0 – depolarization. During the start of the first phase of the ventricular action potential, the cardiomyocyte's resting membrane potential is close to K^+ Nernst EP (-90mV). An excitatory stimulus, normally originating in the SA node then causes a shift in the membrane potential upward, known as depolarization. When the membrane potential reaches -70mV, voltage gated sodium ion channels (I_{Na}) open and Na^+ ions rush into the cell (Ackerman & Clapham, 2004, p. 317). This current is the largest and quickest of all the ion currents causing a rapid up-stroke in the action potential (Figure 1). The size and speed of phase 0 is determined by the number of I_{Na} channels activated.

As phase 0 draws the membrane potential towards Na^+ Nernst EP, Ca^+ currents are activated and influx the cell. This leads to further depolarization as the membrane potential peaks at + 47 mV (Ackerman & Clapham, 2004, p. 318). At this potential the voltage gated Na^+ channel closes and the current ceases.

Figure 1. Ventricular Action Potential. With permission BC Medical Journal 1982;44(2):88.



phase 1 – early rapid repolarization. The transient outward K^+ current (I_{to}) is the first repolarizing current. This current has two subtypes named according to their speed of inactivation and recovery: $I_{to,f}$ inactivates before $I_{to,s}$ (25 to 80 msec v 80 to 200 msec) and recovers much more quickly (25 to 80 msecs v 1-2 seconds) (Ackerman & Clapham, 2004, p. 318). The second type of transient outward current is the calcium activated chloride current ($I_{Cl.Ca}$). Though much smaller than the I_{to} its contribution is not fully understood (Ackerman & Clapham, 2004, p. 318). As transient outward currents are the only currents acting at this time, the cardiomyocyte begins the process of returning to its original resting membrane potential. Phase 1's short rapid period of repolarization results in a notching of the action potential (Figure 1).

phase 2 – plateau. A balance of inward and outward ion current characterizes phase 2. Two types of calcium channels provide the balancing inward current. The smallest of the two currents is supplied by the transient Ca^{2+} channel ($I_{Ca,T}$) and opens at -50mV, peaks at -20mV and closes passively with time. The second and much larger

inward current is supplied by the long lasting Ca^{2+} channel ($I_{Ca,L}$) and opens at approximately -30mV, peaks at 10mV, and also closes passively with time; though hundreds of milliseconds after activation (Ackerman & Clapham, 2004, p. 318). The Ca^{2+} ion movement via the $I_{Ca,L}$ is responsible for cardiac contraction (see electrical-mechanical coupling).

Other ionic movement during phase 2 is generated from the Na^{+} - Ca^{2+} exchanger (NCX). The NCX draws Ca^{2+} either into or out of the cell in a fixed ratio with sodium (1:3). This provides an inward current half the size of that supplied by the $I_{Ca,L}$ (Ackerman & Clapham, 2004, p. 319). Over time the time-dependent Ca^{2+} currents close leaving the outward repolarizing currents.

Three types of outward rectifying potassium currents (I_K) described according to their activation speed and time to reach maximum conductance participate in phase 2 and phase 3 of the action potential: I_{Kr} (rapid), I_{Ks} (slow), and I_{Kur} (ultra-rapid). I_{Kur} role in ventricular repolarization is not fully understood (Ackerman & Clapham, 2004, p. 319), its contribution to atrial repolarization is thought to be much greater (Katz, 2006, p. 406). Upon activation, I_{Kr} and I_{Ks} channels extrude K^{+} from the cell and are the main repolarizing currents, persisting until the membrane potential reaches -40mV.

phase 3 – late rapid repolarization. Three types of outward rectifying potassium currents (I_K) close when the membrane potential reaches -40mV, stopping outward K^{+} flow. Once closed, only the inward rectifying potassium current (I_{K1}) remains. The contribution of I_{K1} to repolarization is controlled by intracellular blockade from magnesium (Nerbonne & Kass, 2003, p. 33; Vandenberg, 1987).

phase 4 – diastolic repolarization. With inactivation of I_K currents, I_{K1} continues to drive the cell towards K^+ Nernst EP. Dominant in phase 4, this channel opens during phase 2 and is active throughout phase 3 of the action potential; though its peak activity is below - 40 mV. Its action is to return the cardiomyocyte to a resting membrane potential. Once the membrane potential is negative to its threshold (-70mV), voltage gates for the Na^+ channel are reactivated, ready for another excitatory stimulus to initiate depolarization. This is important when considering triggers for arrhythmia. Absolute repolarization ceases once the membrane's resting potential reaches approximately -90mV.

Excitation-Contraction Coupling

Excitation-Contraction Coupling (ECC) is the process of converting an electrical stimulus into mechanical action. Structures that penetrate the cardiomyocyte (T-tubules) allow an electrical stimulus to enter the interior of the cell. Entry of electrical stimulus into the cell causes fluctuations in the membrane potential, initiating depolarization. In phase 2 of the action potential Ca^{2+} enters the cell via $I_{Ca,L\ \&\ T}$. Once inside the cell, free Ca^{2+} causes release of stored Ca^{2+} from the sarcoplasmic reticulum via ryanodine receptor channels. This is termed calcium induced calcium release. Released intracellular Ca^{2+} binds to a protein called Troponin, causing a cascade that results in the contraction of the sarcomere. The strength of this contraction is proportional to the level of intracellular calcium released.

With contraction of the sarcomere complete, calcium-adenosine triphosphase pumps (Ca^{2+}-ATPase) return intracellular Ca^{2+} to the SR. The $I_{Ca,L}$ is closed after being

signaled by a regulatory feedback cycle. The NCX extrudes the remaining free Ca^{2+} from the cell, completing the cardiac cycle.

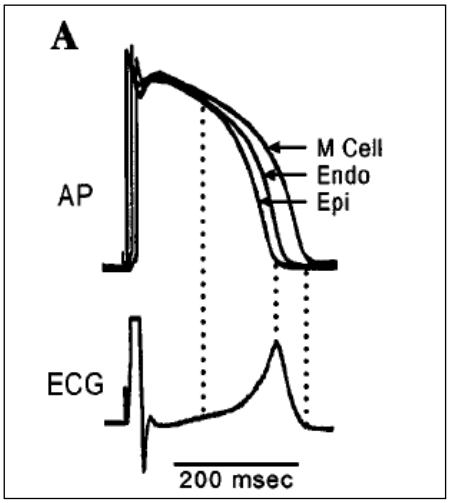
Physiological Differences in Cardiomyocyte Cell Types

Epicardial cells, M cells, and endocardial cells vary in their location within the myocardium and in their physical composition. Within the heart, M cells are most distinctly different from both endocardial and epicardial cells. These are most important in the development of ALQTS and TdP.

Physically, M cells posses a greater sample of I_{to}, I_{Na} and NCX (Zygmunt, Eddlestone, Thomas, Nesterenko, & Antzelevitch, 2001) than endocardial cells and epicardial cells. These increases cause a larger 'spike and dome' appearance on the recorded action potential (Figure 1, phase 1). Additionally, M cells posses less I_{Ks} (Akar, Laurita, & Rosenbaum, 2000; Balati, Varro, & Papp, 1999; Liu & Antzelevitch, 1995), resulting in decreased outward repolarization current during phase 2 and phase 3 of the action potential (Antzelevitch et al., 1991; Anyukhovsky, Sosunov, & Rosen, 1996; Balati et al., 1999). Differences between the endocardial, epicardial, and M cells create 3 slightly difference action potentials (Antzelevitch & Fish, 2001). As a result, when epicardial cells have fully repolarized, endocardial and M-cells are in different stages of repolarization. This is termed heterogeneity of repolarization and is normal in the healthy heart. Heterogeneity of repolarization has been shown in animal models to contribute to T wave inscription on the electrocardiogram (Figure 2). Increases in heterogeneity of repolarization results in the disruption of normal electrical activity and creates an unstable environment within the myocardium. This increases the risk for arrhythmia

(Antzelevitch, 2004); LQTS and TdP are caused by such disturbances. A review of the theoretical framework underpinning ALQTS and TdP follows.

Figure 2. Cardiomyocyte Action Potential Differences Inscribe the T Wave (Antzelevitch & Fish, 2001 with permission)



Theory of Acquired Long QT Syndrome

Risk Factors

Acquired LQTS is a *syndrome* that consists of QT interval prolongation, T wave changes, and TdP, causing syncope and infrequently, death. It is primarily caused by proarrhythmic drug administration but is precipitated by many risk factors.

Currently there are over 60 marketed drugs that have been associated with ALQTS and TdP (Woosley, 2004). Commonly, proarrhythmic drugs interact with protein structures embedded in the sarcolemma, impair function and prolong ventricular

repolarization time. The membrane structures involved vary with each drug, though commonly, all proarrhythmic drugs cause blockage of the I_{Kr} (Fenichel et al., 2004).

The rapid outward rectifying potassium channel's (I_{Kr}) unique composition makes it susceptible to proarrhythmic drug blockade. Two structural changes are responsible for this. The I_{Kr} channel lacks proline residues in the pore portion of the ion channel. These residues normally cause a kinking of the protein. Without proline residues, the pore of the ion channel is proportionally larger than other channels (Mitcheson, Chen, Lin, Culberson, & Sanguinetti, 2000; Recanatini, Poluzzi, Masetti, Cavalli, & De Ponti, 2005). The second characteristic of the I_{Kr} that makes it susceptible to drug blockade is the presence of two aromatic residues that have an affinity for drug binding (Ackerman & Clapham, 2004). Together these characteristics increase the propensity for proarrhythmic drugs to enter, bind and inhibit I_{Kr} function (Antzelevitch, 2004). An example of this affect can be shown with a drug used as a previous exemple, quinidine. Previously described, quinidine is one of the first drugs recognized to have a proarrhythmic affect. However its risk for TdP is dose dependent. At therapeutic levels quinidine, like all proarrhythmic drugs inhibits I_{Kr} (Kao & Furbee, 2005). This results in decreased outward potassium currents during phase 2 and phase 3 of the action potential, causing repolarization time to increase. In this environment TdP can be initiated.

Interestingly, at higher doses of quinidine, the risk of TdP is reduced. High dose administration of quinidine also causes inhibition of I_{Ks} and increases I_{Na} function (Kao & Furbee, 2005). Intuitively one would think that further ion channel interaction would increase the risk for TdP. However, the reduced risk with high-dose quinidine is a result of an interaction between the existing physical properties of endocardial cells, M cells,

and epicardial cells. This interaction results in high dose quinidine causing a reduction in transmural dispersion of repolarization (TDR) and therefore lowers the risk for TdP.

Many risk factors contribute to ALQTS. Concomitant administration of 2 proarrhythmic drugs is one such risk factor. Drug effects can be described by their pharmacodynamic or pharmacokinetic effects. Pharmacodynamic effects occur when one drug amplifies the effect of another drug, while pharmacokinetic effects occur when one drug interferes in the normal metabolism of another drug (Kao & Furbee, 2005). When a drug's proarrhythmic affect is dose-dependent, pharmacokinetic affects causes interference in metabolism, resulting in toxic levels of circulating proarrhythmic drugs (Kao & Furbee, 2005). Many classes of drugs associated with ALQTS produce a pharmacokinetic affect: anti-fungals, antidepressants, anti-retrovirals, calcium channel blockers, antibiotics, and even grapefruit juice (Kao & Furbee, 2005). This latter affect is caused by drugs interfering with the cytochrome P450 enzyme family found in the liver.

Genetic variation in cytochrome (CYP) enzymes can, like polypharmacy result in altered proarrhythmic drug metabolism (Roden & Viswanathan, 2005). For example, it is estimated that 7% of Caucasians and Blacks lack the CYP2D6 enzyme responsible for metabolizing many common drugs (Abedin & Conner, 2007): haloperidol, quinidine, flecainide, amitriptyline, fluoxetine, paroxetine, and methadone (Bryant et al., 2003; Kao & Furbee, 2005). Consequently, instead of metabolizing these drugs, these patients experience an accumulation of the drug, amplifying their risk for proarrhythmia.

ALQTS can also be influenced by age and gender (Benoit et al., 2005; Macfarlane, McLaughlin, Devine, & Yang, 1994; Mason et al., 2007; Sugao et al., 2006).

During childhood the QT interval is equal between sexes. After puberty, possibly due to hormonal changes, the QT interval duration of men decreases. This difference persists over the entire lifespan (Pearl, 1996; Rautaharju et al., 1992). In addition to natural lengthening with age, it is estimated that women have a QT interval 2-6% greater than that of men (Sugao et al., 2006).

Several diseases are also associated with risk for QT interval prolongation. Congestive heart failure and coronary artery disease change cardiomyocyte structure and function, resulting in abnormal ventricular repolarization (Cha & Shen, 2008). Diseases of the hepatic and renal systems alter the metabolism and elimination of proarrhythmic drugs (Gussak & Gussak, 2008), while subarachnoid hemorrhage (Zaroff et al., 2006b), thyroid disease (Colzani et al., 2001b), and diabetes (Veglio, Chinaglia, & Cavallo-Perin, 2004) are also linked to QT interval prolongation, though the mechanisms are less clear.

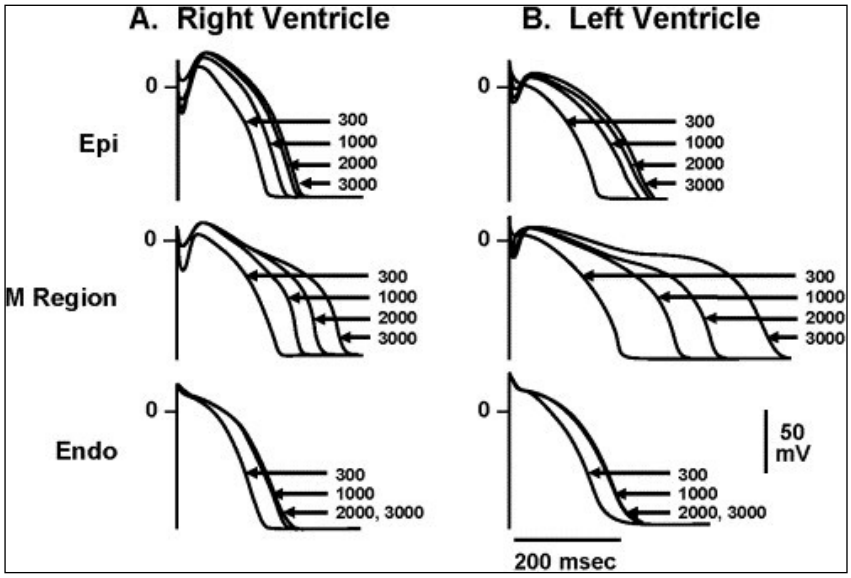
In addition to age, sex, and diseases, electrolyte disturbances are major contributors to ALQTS. Decreased K^+ causes QT interval prolongation by directly reducing outward K^+ currents that are prominent in phases 1-3 of the action potential (Kannankeril & Roden, 2007). Similarly, decreased Ca^{2+} causes an increase in the duration of phase 2 of the action potential; a direct result of delayed calcium activation (Bradley, Metzger, & Sanatani, 2004). Intracellular magnesium (Mg^+) differs from K^+ and Ca^{2+} as it has various functions. Its utility in treating arrhythmias like TdP is possibly due to its potentiating affect on I_{K1} and the Na^+-K^+ exchange pump, resulting in increased cellular K^+ (Kao & Furbee, 2005). Hypomagnesemia increases I_{K1} permeability and disrupts calcium reuptake in the sarcoplasmic reticulum (Michailova, Belik, &

McCulloch, 2004) leading to increased cellular sodium and calcium. Taken together hypokalemia, hypocalcemia, and hypomagnesia contribute to ALQTS.

Thus far 12 genes have been associated with CLQTS, but subclinical mutations in these genes also pose a risk for ALQTS. This is known as incomplete penetrance. For CLQTS it is estimated that QT interval prolongation is present in only 62-90% of mutation carriers, these patients are also at risk for ALQTS (Medeiros-Domingo, Iturralde-Torres, & Ackerman, 2007). Also 20% of patients with ALQTS may possess an undetected mutation in a LQTS gene region (Lehtonen et al., 2007; Paulussen et al., 2004; Yang et al., 2002). The most common gene regions associated with abnormal ventricular repolarization are those encoding the I_{Ks}, I_{Kr}, and I_{Na} (Tester, Will, Haglund, & Ackerman, 2005). These mutations reduce repolarization reserve and greatly increase the risk for developing QT interval prolongation. The concept of repolarization reserve will be discussed further on.

Finally, physical differences between myocardial cells also contribute to ALQTS. Long cardiac cycles, as occurs with bradycardia and long pauses, are associated with an increased risk for A-LQTS (Amchentsev et al., 2008; Ashworth, Levsky, Marley, & Kang, 2005). In experiments, Anzelevitch and colleagues have shown that decreasing cardiac stimulatory rates results in action potential prolongation for all myocardial cell types, but preferentially M cells (Antzelevitch, 2005b; Antzelevitch et al., 1991). Additionally due to distribution differences, repolarization differences are evident between the left and right ventricles (Figure 3). Transmural and spatial differences contribute greatly to the development of ALQTS and TdP. This contribution will be discussed in the following section.

Figure 3. Heterogeneity of Repolarization (Antzelevitch & Fish, 2001 with permission)



The risk for developing ALQTS differs for each patient. This makes prediction and therefore prevention, difficult. All proarrhythmic drugs block I_{Kr}, however a patient's ventricular repolarization response is highly individual, and is based largely on the presence of associated risk factors: age, sex, concomitant diseases, electrolyte disturbances, poly-pharmacy, bradycardia, and genetic predisposition. The theory of repolarization reserve helps to explain why some patients develop QT interval prolongation after administration of a proarrhythmic drug, while others do not.

Theory of Repolarization Reserve

Repolarization reserve was first coined by Roden (1998) and explains how the heart maintains a normal level of functioning when its capacity to function has been altered by congenital or acquired factors. As a theory, repolarization reserve has only recently been confirmed. Using an animal model, Xiao and colleagues (2008) artificially reduced I_{Kr} current while recording I_{Ks} current. They showed that the I_{Ks} current increased in response to a sustained reduction in I_{Kr} current. Translating these findings, when an otherwise healthy patient is given a proarrhythmic drug, there is a blocking of the I_{Kr} current. The I_{Ks} current in this patient would then increase to compensate, ensuring that outward repolarizing currents are maintained. In a patient with sufficient repolarization reserve, compensation results in a normal QT interval duration.

In an opposing example, a patient possessing a sub-clinical lesion in the KCNE1 gene region is administered a proarrhythmic drug. Commonly, drug administration results in blockage of I_{Kr} current. In healthy individuals, I_{Ks} current would upregulate in an effort to compensate for the loss of I_{Kr} current. However this patient has an existing mutation in the KCNE1 gene, resulting in reduced I_{Ks} current. Therefore, compensation for loss of I_{Kr} current is not possible; there is a net decrease in outward rectifying repolarization currents and prolongation of the QT interval on electrocardiogram.

Of patients developing QT interval prolongation, only a portion progress to developing the signs and symptoms of ALQTS: T wave changes, long pauses, TdP, syncope, and less commonly, death. A large determining factor for the progression to ALQTS is heterogeneity of repolarization.

Ventricular Repolarization and ALQTS

Transmural Voltage Gradients

Heterogeneity of repolarization exists naturally within the myocardial wall. When the myocardial cell type's action potentials are overlaid, clear differences exist (Figure 3). When epicardial cells have fully repolarized, endocardial and M-cells are in different stages of repolarization. This is termed transmural dispersion of repolarization (TDR).

The unequal distribution of myocardial cell types throughout the heart contributes to TDR. M-cells are unique in their electrophysiological properties, possessing much longer action potential durations than endocardial and epicardial cells. M-cells are unevenly distributed throughout the heart and have been localized in the subendocardium to midmyocardium portion of the anterior wall, deep subepicardium to mid myocardium portion of the lateral wall, right ventricular outflow tracts, interventricular septum, and throughout the endocardial structures (Antzelevitch & Fish, 2001; Antzelevitch & Nesterenki, 2003). Consequently, in addition to TDR, the irregular distribution of myocardial cell types lead to spatial differences in repolarization: interventricular, interseptal, and apicobasal regions (Brunet et al., 2004; Pitruzzello, Krassowska, & Idriss, 2007; Volders et al., 1999). These differences exist without complication in the normal functioning heart.

When patients develop QT interval prolongation in response to proarrhythmic drugs or noxious stimuli, only a subset of patients develop ALQTS. A determining factor in the development of ALQTS is the relative homogeneity or heterogeneity of ventricular repolarization.

Homogenous changes to Transmural Dispersion of Repolarization

The physical properties of endocardial cell, M cells, and epicardial cells results in varied responses to noxious stimuli. M cells possess less I_{Ks} than epicardial and endocardial cells (Akar et al., 2000; Antzelevitch & Fish, 2001; Balati et al., 1999). Therefore when there is a blocking of $I_{Ks,}$ the action potential of endocardial cells and epicardial cells prolong, due to significant decreases in outward repolarizing current. But the action potential of M cells remains relatively unchanged due to a relatively small sample of I_{Ks} (Antzelevitch, 2005b). The QT interval may be prolonged in this scenario, but due to physical cell differences, the TDR is actually reduced. This is an important concept.

Anzelevitch and colleagues (2004; 2000) attempted to induce TdP in an animal model with artificially reduced TDR: they were unsuccessful. They introduced isoproterenol, a beta agonist, causing a preferential increase in the action potential of M cells, and therefore increasing TDR. Anzelevitch and colleagues then re-attempted to induce TdP and were successful (Shimizu & Antzelevitch, 2000). Consequently, QT interval prolongation with normal or reduced TDR possesses only a small to nil risk for TdP. Drugs associated with reduced TDR are sodium pentobarbital, amiodarone, and verapamil.

Heterogenous changes to Transmural Dispersion of Repolarization

Two main outward currents participate in phase 2 of the action potential, I_{Kr} and I_{Ks}. With the administration of a proarrhythmic drug, blockade of I_{Kr} commonly occurs, leaving I_{Ks} as the dominating outward current. It is shown that I_{Ks} up-regulates to

compensate for the loss of I_{Kr} (Xiao et al., 2008). In the endocardial and epicardial cells this upregulation is effective, with very little change in action potential duration. However in M-cells with less sample of I_{Ks}, compensation cannot occur. Drugs that block I_{Kr} or I_{Ks}, or increase I_{Ca} or I_{Na}, therefore preferentially increase M cell action potential duration (Anzelevitch, 2008). As the distribution of M cells vary throughout the heart, proarrhythmic drugs also cause increases in spatial dispersion of repolarization (SDR).

spatial dispersion of repolarization. Repolarization within the heart, although coordinated, is not in unison, even in normal functioning. Spatial dispersion of repolarization (SDR) refers to differences in repolarization duration across the left ventricular wall (transmural), between the left and right ventricle (interventricular), and between the base and apex of the heart (apico-basal) (Akar et al., 2000). Spatial differences develop secondary to TDR, creating the necessary environment for TdP (Antzelevitch, 2005a).

electrocardiographic signs. On the electrocardiogram the peak of the T wave is inscribed by repolarization of epicardial cells and is terminated by repolarization of M cells (Antzelevitch & Fish, 2001). Therefore, the distance between the peak and the end of the T wave represents the differences in repolarization time between the different myocardial cell types. As such the T_{peak}-T_{end} interval has been postulated to be a non-invasive marker for TDR. Researchers are attempting to validate this.

An electrocardiographic sign of increased SDR is T wave alternans. Alteration in T wave morphology arises from spatial differences in islands of neighboring cells (Chinushi, Restivo, Caref, & El-Sherif, 1998; Pruvot & Rosenbaum, 2003, p. 518). When

normal repolarization gradients within the myocardium change, an every-other-beat phenomenon known as T wave alternans develops (Pruvot & Rosenbaum, 2003, p. 519). In normal repolarization producing an upright T wave, the epicardial, endocardial and M-cells repolarize in order. However, repolarization changes that produce negative T waves are caused by M-cells repolarizing first, followed by endocardial cells, and finally epicardial cells (Shimizu & Antzelevitch, 1999). As T wave alternans is caused by changes in repolarization gradients, it is a useful electrocardiographic sign for the development of an environment that is susceptible for TdP.

Torsades de Pointes, the arrhythmia most likely associated with ALQTS, is an opportunistic arrhythmia, occurring in an environment of abnormal repolarization. This is primarily described as being global repolarization prolongation, increased TDR, and increased SDR. For the clinician, electrocardiographic evidence of these include, QT interval prolongation, increased T_{peak} - T_{end}, and T wave alternans. Standards for the later two have not been established, or like QT interval prolongation, shown to be predictive of TdP. As such monitoring the QT interval remains the only clinical tool for preventing TdP.

Torsades de Pointes

Triggering

After-depolarizations are small oscillations in the cardiomyocyte membrane that have the potential to trigger ectopic beats (Kao & Furbee, 2005). Early-after-depolarizations (EADs) are classified according to their onset within the action potential; phase 2 EAD's occur above a membrane potential of -30mV, while phase 3 EADs occur

below a membrane potential of -30mV (Antzelevitch, Burashnikov, & DiDiego, 2003, p. 206). Early-after-depolarizations result from sudden inward shifts of current during the later phases of the action potential (Antzelevitch, Burashnikov, & Di Diego, 2008, p. 74). These shifts are most commonly carried by the $I_{Ca,L}$ (Antzelevitch, Burashnikov et al., 2003, p. 209).

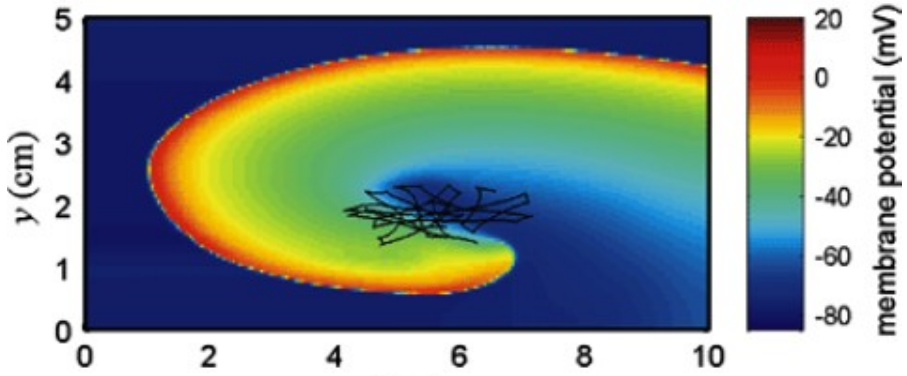
Delayed-afterdepolarizations (DADs) occur later in the action potential (phase 4) (Antzelevitch et al., 2008, p. 72). In an environment of high intracellular calcium, stimulation by nonselective cationic currents (I_{ns}), NCX, or $I_{Cl.Ca}$ (Antzelevitch, Burashnikov et al., 2003, p. 211; Sipido, Bito, Antoons, Volders, & Vos, 2007), causes membrane oscillations and possibly further calcium induced calcium release from the sarcoplasmic reticulum (Antzelevitch et al., 2008, p. 76). Both EADs and DADs can, if beyond threshold, cause cardiomyocyte depolarization (Antzelevitch, Burashnikov et al., 2003, p. 205) and in susceptible environments, cause arrhythmia. This is known as a triggering and occurs before an episode of TdP.

Sustaining

Once TdP is triggered by an afterdepolarization a mechanism needs to be in place for it to be maintained. This mechanism is called re-entry and for TdP, *spiral waves* are thought to be most probable (Antzelevitch, Burashnikov et al., 2003, p. 216). A spiral wave is formed by a triggered wavefront crossing the repolarization path of a previously conducted beat. Non-refractory cells advance the wavefront, progressively exciting cells previously refractory to stimulation. An area of lagging repolarization curves the wavefront towards newly excited cells (Figure 4). The head and tail of the spiral wave is

formed by the excitatory wave front meeting refractory cells (Comtois et al., 2005). For TdP, the spiral wave front is slightly unstable and rotates around a non stationary region. This creates beat-to-beat differences in axis and amplitude that are responsible for generating the characteristic polymorphic patterning that is seen with TdP (Starmer et al., 1995). Re-entry wavefronts continue until the spiral wave's activation front is disrupted by either a sample of refractory cells that cannot propagate the re-entry signal, or by instability fragmenting the wave front. In these scenarios the outcome is either non-sustained TdP or in the case of the later scenario, ventricular fibrillation (Starmer et al., 1995).

Figure 4. Spiral Activation Wave Front (Comtois, Kneller, & Nattel, 2005, by permission of Oxford University Press)



Summary

Acquired long QT syndrome occurs with administration of proarrhythmic drugs, in association with existing risk factors. The theory of repolarization reserve explains how a reduction in repolarizing current occurring as a result of drug administration, can result in a normal QT interval. A two hit scenario resulting in the depletion of

repolarization reserve, further explains why some individuals develop QT interval prolongation in response to proarrhythmic drug administration, while others do not. As a syndrome, QT interval prolongation alone is not enough to cause ALQTS and TdP.

The heterogeneity of repolarization is an important factor in determining whether patients progress to TdP or not. Homogenous changes in ventricular repolarization, as seen with drugs such as amiodarone, are of low risk for TdP, due to reduced TDR. Other drugs, like flecainide and dofetilide, potently increase differences in TDR and consequently possess much greater risk. This effect is due to the physical characteristics of M cells, resulting in preferential prolongation in action potential duration in these cells versus endocardial and epicardial cells. This development leads to critical increases in TDR and SDR.

In a susceptible environment, early-after-depolarizations can be initiated, and if above threshold, trigger ectopic beats. With increased TDR and SDR, an aberrant beat can trigger a spiral wave front that provides the re-entry mechanism that produces the characteristic polymorphic patterning seen with TdP. This spiral wave front continues to propagate the arrhythmia until it reaches an island of refractory cells and self-terminates, or splinters into disorganized activity, causing ventricular fibrillation. The end point of this activity for the patient if not terminated early, is death.

Conclusion

Acquired LQTS is predominately caused by proarrhythmic drug administration in association with QT interval prolonging risk factors. Whether a patient develops QT interval prolongation, progresses to ALQTS and/or develops TdP, is highly individual

and can be explained by the two hit theory first postulated by Roden, repolarization reserve. To prevent TdP, clinicians need to be adept in monitoring for signs and symptoms of disorganized electrical activity. This requires the clinician to be skillful and knowledgeable in all facets of QT interval monitoring. A review of the literature demonstrates that there a many gaps in our understanding of the need for QT interval monitoring and the risk for developing ALQTS and TdP in hospital based patients receiving cardiac monitoring. A review of the ALQTS literature follows.

Review of the LQTS Literature

Over the last twenty years researchers have attempted to establish the predictiveness of QT interval prolongation. It has been shown to be linked to adverse outcomes, though not predictive of TdP. The AHA has recommended that the QT interval be measured in patients that are administered or have overdosed on a proarrhythmic drug, have bradycardia or long pauses, or experience electrolyte disturbances. In the hospital based sample receiving cardiac monitoring, it is unknown how many of these patients require QT interval monitoring as per the AHA practice standards (Drew et al., 2004), develop QT interval prolongation, or experience adverse in-hospital events. The usefulness of this type of monitoring in the hospital setting is yet to be established. The following is a review of the literature as it pertains to the ability of clinicians to perform QT interval monitoring, the prevalence and factors contributing to QT interval prolongation, and the associations between QT interval prolongation and adverse events.

Baseline Nurses QT Interval Related Knowledge

Research evaluating the ability of nurses to perform QT interval monitoring, is limited. Studies conducted to date have been primarily conducted with physician samples (Table 1). One study incorporated a nursing subgroup (LaPointe, Al-Khatib, Kramer, & Califf, 2003). In this study nurses consisted of 45% (n=149) of the total sample but were not analyzed as a sub-group. Overall, less than half of the participants were able to correctly measure the QT interval (43%); 60% of physicians performed this measure correctly. Qualitatively nurses were thought to be "very uncomfortable with measuring/documenting a QT interval and calculating a QTc…we actually developed a

table for them to use…so they would not have to use a formula…but they were still reluctant to document their measurements and calculations" (LaPointe, personal communication, May 16, 2008). A lack of knowledge could underpin this fear. A Canadian study of 180 nurses evaluating the frequency of QT interval monitoring revealed that 70% 'sometimes measure' or 'never measure' the QT interval (Hutton, 2008). When asked why they do not regularly monitor the QT interval, 70% cited a "lack of knowing" as the main reason.

Table 1. Studies Evaluating QT Interval Skill

Author	Year	Skill	n	Sample	QT	QTc
Montgomery	1994	Mark QT	158	**Overall** Emergency MD Cardiology Cardio Thoracic MD General physicians	**24%** 0% 43% 14% 28%	NA
La Pointe	2003	Measure QT	334	**Overall** Physicians Residents Nurses Other	**42%** 60%	NA
Al-Khatib	2005	Measure QT	517	**Overall** Attend. physicians Residents Medical Students Nurses Physician assistants Pharmacists unknown	**43%**	NA
Marshall	2005	Measure QT State QTc - formula	40	**Overall** Physicians Resident Physicians	**65%** 60% 70%	 15% 25%
Viskin	2005	Measure QT Calculate QTc	877	**QT experts (GS)** Arrhythmia experts Cardiologists Non Cardiologists	 89% 84% 65%	 80% <50% <40%
Pickham	2007	Measure QT Calculate QTc	33	Nurses	61%	0%
Solomons	2008	Measure QT Calculate QTc	64 -	**Overall** Senior physicians Special. physicians Generalist	**10%**	5%

In preparation for this investigation, a cross-sectional pilot study was conducted assessing the QT interval related knowledge of Nurse Practitioner (NP) and Clinical Nurse Specialist (CNS) students enrolled in graduate a nursing program at a large west coast university (Pickham & Drew, 2007). All participants ($N = 33$) were experienced critical care and acute care Registered Nurses ($M = 7.6$, $SD = 6.4$, *range* = 1.5 – 25 years). From this small sample, 61% were able to correctly measure the QT interval, but all were unable to perform a QT interval calculation; one student attempted but was incorrect. Interestingly, 73% of participants indicated that they measure the QT interval in their practice regularly. We did not ask nurses which method they used to monitor the QT interval: manual, semi-automated, automated.

Studies with physician samples reveal a similar level of competence. In an early study, Montgomery and colleagues (1994) assessed the ability of 158 physicians to mark the QT interval on a sample rhythm strip. In this sample, no emergency room physicians, less than half of the cardiologists, and less than one third of general physicians correctly marked the QT interval. Overall, only 24% of physicians were able to mark the QT interval correctly. To be fair, this could be attributed to the lack of QT interval related knowledge at this time. In 1994 the need for QT interval monitoring was not as evident as it is today. Later studies are a better reflection of current physician competence.

Viskin et al. (2005) performed the largest study of QT interval knowledge thus far. An international sample of physicians ($N = 877$) with varying expertise were asked to measure the QT interval and QTc intervals of 4 electrocardiograms, and classify them as being prolonged or normal: 2 were of LQTS subjects and 2 were of normal subjects. Classifications performed by QT interval experts ($N = 25$) acted as the gold standard.

From this sample, physicians identifying themselves as cardiologists and those identified as non-cardiologists performed worse than those identifying themselves as arrhythmia experts. Only 36% of the cardiologists and 31% of the non-cardiologist physicians correctly identified the 2 LQTS patients, and less than 25% correctly classified all 4 electrocardiograms.

In a recent study of 64 psychiatrists only 10% of the sample could measure the QT interval and only 5% of these could correctly perform a QT interval corrected for heart rate (QTc) (Solomons, Treloar, & Noronha, 2008). As many psychiatric drugs have proarrhythmic effects, this study suggests that psychiatrists lack the skills needed to effectively monitor their patients for ALQTS and TdP. Studies with other physician samples are in line with these results (Al-Khatib et al., 2005; Marshall & Myles, 2005).

An important consideration to make when interpreting these studies is that the tools used to assess QT interval ability are not representative of clinical practice. In clinical practice, clinicians perform QT interval monitoring with automated and semi-automated tools that are built into electrocardiographs and bedside monitoring devices. These produce more than 1 channel for analysis, and with electrocardiograms, an automated QT interval measurement. When a participant in a research study is asked to perform a QT/QTc interval measurement, he or she is often asked to perform this measurement manually in a single lead rhythm strip. Without the aid of computers to manipulate the rhythm strip, paper speed, or Q wave and T wave on and offset, these methods result in significantly lower levels of QT interval monitoring proficiency than would be seen in clinical practice. Collectively however, initial evidence suggests that the majority of clinicians do not possess the knowledge and skills necessary to perform QT

interval monitoring accurately and reliably. As nurses provide continuous cardiac monitoring of critical care patients, a large scale study specifically assessing their ability to perform QT interval is needed.

QT Interval Prolongation

The QT interval is a surrogate marker for ventricular repolarization. Prolongation is a sign of abnormalities in ventricular repolarization that creates an environment that is susceptible for the development of arrhythmia, specifically TdP. To prevent this from occurring clinicians should monitor the QT interval for electrocardiographic signs of cardiac instability. Though, the reliability of this monitoring is questionable.

One aspect of variability in monitoring is in the application of QT interval correction formulae. Research has shown that QT interval correction formulas act differently (Malik, 2001). This was recently evident in a study of HIV patients. Using the Bazett's correction formula, Charbit and colleagues (2009) determined that 13.5% of patients had a QT interval greater than 500 milliseconds (ms), however when the Fridericia formula was applied to the data, QT interval prolongation was evident in only 4% of the sample. Universal standards for correcting the QT interval have not been firmly established.

Besides correcting for heart rate, the threshold for QT interval prolongation is another contentious aspect of QT interval monitoring. Threshold limits in studies attempting to establish prevalence are either arbitrarily set, or are based on the study's population distribution. Benoit and colleagues (2005) established their QT interval prolongation threshold as being greater than the 95th percentile; this was equal to 463 ms

for women and 454 ms for men. Of the studies establishing a threshold (Table 2), 8 different thresholds have been used to define QT interval prolongation, ranging from 420 msecs to 500 msecs. Due to known QT interval differences between sexes, four studies established separate sex-based thresholds (Charbit et al., 2009; Chugh et al., 2009; Dumontet et al., 2006; S. M. Sohaib, Papacosta, Morris, Macfarlane, & Whincup, 2008). The various thresholds lead to obvious differences in QT interval prevalence rates.

As one expects, a lower threshold for QT interval prolongation, results in higher reported prevalence rates. Ehret and colleagues demonstrated this in their study of patients using methadone. In this study, a threshold of 460 ms resulted in 29.9% being classified as having QT interval prolongation. This fell considerably to 16.2% when the threshold for QT interval prolongation was raised to 500 ms (Ehret et al., 2006). The aim of establishing a threshold for QT interval prolongation is to determine one's risk for TdP; but what best predicts this risk?

An important aspect when attempting to answer this question is that the risk associated with a prolonged QT interval is not absolute. A patient with a QT interval greater than 480 ms may show signs of ALQTS, while many others do not. Inversely, a patient may have a QT interval of 600 ms and experience no adverse effects. The theory of repolarization reserve explains this phenomenon. Currently there is no consensus as to what is the threshold for QT interval prolongation. A QT interval greater than 500 ms is considered by many to be of concern (Drew et al., 2004). In studies using a threshold for QT interval prolongation of 500 ms, prolongation rates varied from 0.63% (Sohaib et al., 2008) to 13% (Chugh et al., 2009) and 16.2% (Ehret et al., 2006). These varying prevalence rates can be attributed to differences between the study samples.

Table 2. Study Thresholds for QT Interval Prolongation

Study	Author	Year	n	Threshold for QTc prolongation
Framingham	Goldberg	1991	5125	Bazetts > 440 msecs
Zutphen	Dekker	1994	vary	Bazetts > 420 msecs
Strong Heart	Okin	1999	1839	Bazetts > 460 msecs
NHNES III	Brown	2001	5833	Bazetts > 440 msecs
SAH	Fukui	2003	100	Bazetts > 470 msecs
Kohala HRP	Grandinetti	2004	1415	Bazetts > 440 msecs
NHNES III	Benoit	2005	8367	Fridericia (95^{th} %) Women > 463 msecs Men > 454 msecs
Psychiatric pop.	Dumontet	2006	88	Bazetts Women > 460 msecs Men >450 msecs
Methadone pop.	Ehret	2006	247	Bazett > 460 msecs
EURODIAB	Giunti	2007	1415	Bazetts > 440 msecs
British Heart	Sohaib	2008	3596	Hodges > 440 msecs
HIV pop.	Charbit	2009	978	Fridericia Women > 450 msecs Men > 440 msecs
Hypertension pop.	Salles	2009	538	Bazett (primary) Fridericia Hodges Framingham >460 ms
Methadone pop.	Anchersen	2009	200	Bazetts > 470 msecs
Acute geriatric pop.	Lubart	2009	422	Bazetts Women > 470 msecs Men > 450 msecs
Oregon SCD	Chugh	2009	309	Bazetts Women > 470 msecs Men > 450 msecs

variables. Besides the methods used for measurement, heart rate correction, or threshold for QT interval prolongation, studies have identified many patient specific variables that are significantly associated with QT interval prolongation (Table 3).

Table 3. Predictors of QT Interval Prolongation

Study	Author	Year	Sample	Determinants of QT	
NHNES III	Brown	2001	5833 >40 years	Age & Sex Diabetes Glucose intolerance Fasting insulin C-peptide Hypertension Cholesterol Obesity	
SAH	Fukui	2003	100 SAH 21–82 years	**Univariate** Sex Potassium Calcium Glucose	**Multivariate** Sex Potassium
Kohala HRP	Grandinetti	2004	1415 >18 years	**Multivariate** Sex 2-h fasting glucose Systolic BP Ethnicity	
NHNES III	Benoit	2005	8367 >40 years	**Univariate** Age Potassium Hypertension Myocardial Infarction *Proarrhythmic drug Men*Hypocalcemia Women*Increased weight Women*Diabetes	**Multivariate** Age History of Thyroid dx. Proarrhythmic drug Men*Hypocalcemia Men*Myocardial Infarction Women*Hypokalemia
Chinese HT	Peng	2006	1480 21-65 years Hypertensive	Systolic BP * Sex Diastolic BP * Sex	
Psychiatric pop.	Dumontet	2006	88 Psych. pt >60 years	Sex & Age Group Proarrhythmic drug Myocardial Infarction	
EURODIAB	Giunti	2007	1415 T1 Diabetes Mean 14yr	**Multivariate** Age & Female sex HA1C Systolic BO Body Mass Index Physical Activity (protective) Women*Body Mass Index	
HIV pop.	Charbit	2009	956 HIV	Age & Sex Ethnicity (white) ECG abnormalities Time of infection > 4yrs Heart Rate (with Bazett)	
Oregon SCD	Chugh	2009	403 CAD 309 controls	Sex Diabetes Proarrhythmic drug Diabetes* proarrhythmic drug	

Common to most studies, and widely accepted is the significant differences in QT interval length between sexes. Consequently women are at greater risk for QT interval prolongation (Benoit et al., 2005; Brown, Giles, Greenlund, Valdez, & Croft, 2001; Charbit et al., 2009; Chugh et al., 2009; Fukui et al., 2002; S. Fukui et al., 2003; S. Giunti et al., 2007; Grandinetti, Seifried, Mor, Chang, & Theriault, 2005; Peng et al., 2006). This has been estimated to be by as much as 6% (Sugao et al., 2006). In studies, women possess 9 – 13 ms longer mean QT intervals than men (Benoit et al., 2005; Charbit et al., 2009; Chugh et al., 2009).

Age is also significantly associated with QT interval prolongation in the majority of studies (Benoit et al., 2005; Brown et al., 2001; Charbit et al., 2009; Sara Giunti et al., 2007). This was best demonstrated by Brown and colleagues (2001) who stratified their sample into 4 groups. In the lowest age group, less than 45 years, QT interval prolongation was evident in 19.1%. This increased with each subsequent age group, 25.3% of those 45 - 55 years, 31.1% of those 55 - 65 years, and 39.2% of those older than 65 years.

In addition to female sex and advancing age, certain diseases have also been significantly associated with QT interval prolongation; diabetes (Benoit et al., 2005; Brown et al., 2001; Chugh et al., 2009; S. Giunti et al., 2007), subarachnoid hemorrhage (Fukui et al., 2003), HIV (Charbit et al., 2009), hypertension (Benoit et al., 2005; Brown et al., 2001; Charbit et al., 2009; S. Giunti et al., 2007; Grandinetti et al., 2005; Owecki, Michalak, Nikisch, & Sowinski, 2006; Peng et al., 2006), hypothyroidism (Benoit et al., 2005) and coronary artery disease (Chugh et al., 2009). Many of the markers for these diseases have also been independently associated with QT interval prolongation.

Additionally, contributors to diseases such as obesity, body mass index, and physical activity have also been shown to be independently associated with QT interval prolongation (Brown et al., 2001; Giunti et al., 2007).

With age, sex, and disease, abnormal electrolyte levels are also independently associated with QT interval prolongation; most commonly potassium (Benoit et al., 2005; Fukui et al., 2003). In one study, this relationship was dependent upon sex. Benoit and colleagues (2005) shows that hypocalcemia is associated with QT interval prolongation in men, but not women, while hypokalemia was associated with QT interval prolongation in women but not men. These were not the only interactions to exist in the literature. Other interactions were diabetes and proarrhythmic drug administration (Chugh et al., 2009), body mass index and female sex (Giunti et al., 2007), and myocardial infarction and male sex (Benoit et al., 2005).

In summary, the prevalence of QT interval prolongation is dependent upon the population being studied. Using different QT interval correction formulae or thresholds for QT interval prolongation changes the prevalence. The prevalence of QT interval prolongation in patients admitted to a hospital unit requiring cardiac monitoring is unknown. Many variables are present in admitted patients that were independently associated with QT interval prolongation. Therefore, the critical care population may have a higher prevalence of QT interval prolongation than that found in previous studies (Table 4). Establishing this prevalence is a primary aim of this investigation.

Table 4. Prevalence of QT Interval Prolongation.

Study	**Author**	**Year**	**Mean QTc Interval**	**% Prolonged**
Framingham	Goldberg	1991	Women = 401 msec Men = 385 msec	**Overall** 5.4% Women 7% Men 2%
Zutphen	Dekker	1994	410 msecs	35%
Strong Heart	Okin	1999	Alive = 429 msecs Dead = 441 msecs	10.3%
NHNES III	Brown	2001	428 msecs	Women 36.7% Men 18.5%
SAH	Fukui	2003	466 ms	16%
Kohala HRP	Grandinetti	2004	Not stated	Women 25.4% Men 16.2%
NHNES III	Benoit	2005	Women = 426 ms Men = 417 ms	Women 6% Men 6.7%
Psychiatric	Dumontet	2006	Not stated	Women 21.4% Men 29.4%
Methadone	Ehret	2006	440 msecs	29.9%
EURODIAB	Giunti	2007	420 msecs	18.7%
British Heart	Sohaib	2008	419 ms	19%
HIV	Charbit	2009	418 msecs	13.5%
Hypertension	Salles	2009	Not stated	29%
Methadone	Anchersen	2009	Not stated	15%
Geriatric	Lubart	2009	423 msecs	27%
Oregon	Chugh	2009	Women = 457 Men = 446	13%

QT Interval Prolongation and Adverse Outcomes

Many studies have investigated the association between QT interval prolongation and risk for all-cause mortality, sudden cardiac death, cardiovascular disease related mortality and time to adverse events, such as first myocardial infarction (Table 5). In these studies single 12 lead electrocardiograms are used for data collection, and commonly QT interval duration is determined with manual measurement using a Bazett's correction formula. The threshold for QT interval prolongation also varies widely from 420 msecs to 480 msecs.

Table 5. QT Interval Prolongation and Association with Adverse Events

Study	Author	Year	Endpoint	QT Interval Prolongation and Endpoint
Framingham	Goldberg	1991	1.All cause mortality 2.SCD within 1 hr 3.CAD related death	Not predictive
Zutphen	Dekker	1994	1.Time to 1st MI 2.CHD related death 3.SCD within 2hrs	1.2.3 (*HR* = 0.9 - 5.7) ns 2.3.1 (*HR* = 1.3 - 7.6) 3.3.7 (*HR* = 1.3 - 10.9)
Strong	Okin	1999	1.All cause mortality 2.CVD related death	Adjustment 1.2 (*RR* = 1.3 – 3) 2.2.1 (*RR* = 1.0 – 4.4) ns
SAH	Wong	2003	1.All cause mortality 2.Cardiac related death	1. 3.2 (*RR* = 1.9 – 5.4) 2. 4.1 (*RR* = 1.7 – 9.8)
Cardiovascular	Robbins	2003	1.All cause mortality 2.CHD related death	Adjusted 1. 1.34 (*RR* = 1.07 - 1.67) 2. 1.6 (*RR* = 1 – 2.5) ns
ARIC	Dekker	2004	1.CVD event = MI 2.CVD related death 3.All cause mortality	Adjusted 1.1.55 (*RR* = 1.08 – 2.23) 2. 2 (*RR* = 1.07 – 3.75) 3.1.33 (*RR* = 0.95 – 1.87) ns
Rotterdam	Straus	2006	1.SCD within 1 hr	Adjusted Men 2.6 (*HR* = 1.1 – 5.8) Women 2.5 (*HR* = 1.0 – 7.1) ns
Women's HI	Rautaharju	2006	1.CHD events 2.CHD related mortality	Adjusted. 1. 1.37 (*HR* = 1.08 – 1.73) 2. CVD 1.9 (*HR* =1.09 – 3.33)
British Heart	Sohaib	2008	1.All cause mortality 2.CVD related death 3.1st MI 4.1st CVA	Adjusted 1.1.33 (*HR* = 1.11 - 1.59) 2.1.32 (*HR* = 1.01 – 1.72) 3.1.42 (*HR* = 1.07 – 1.89) 4. 0.99 (*HR* = 0.69 – 1.42) ns
Hypertension	Salles	2009	1.CVD related event 2.All cause mortality 3.CVD related death	1.1.68 (*HR* = 1.09 – 2.58) 2. 1.12 (*HR* = 0.64 – 1.96) ns 3. 1.56 (*HR* = 0.78 – 3.09) ns
Oregon	Chugh	2009	Sudden Cardiac Death	Univariate 1.2.5 (OR 1.7 – 3.6)

RR = Risk Ratio, *HR* = Hazard Ratio, ns = Not significant

An early study evaluating the association of QT interval prolongation and the risk for adverse outcomes was conducted as part of the large Framingham study (Goldberg et al., 1991). After a follow-up period of 30 years study investigators found no significant statistical relationship between QT interval prolongation beyond 440 msecs and risk for

all cause mortality, sudden cardiac death, or coronary artery disease related mortality. This finding is not supported by other studies.

The Framingham study initially collected data from healthy volunteers, excluding patients with existing coronary artery disease and those taking medications known to prolong the QT interval. Consequently this cohort, at baseline, was relatively homogenous, with only 5.4% possessing a QT interval beyond 440 msecs (Goldberg et al., 1991). During the following 30 year period after baseline data collection, many environmental and genetic factors may have interplayed, contributing to the development of many different diseases in this sample. When researchers attempted to evaluate the association between adverse events and a QT interval collected 30 years prior, at a time when subjects were younger and healthier, no significant association was found.

Subsequent studies have contradicted Framingham's results, finding a significant association between QT interval prolongation and all cause mortality. Okin and colleagues (2000) studied 1839 American Indians, finding that those with a QT interval duration greater than 420 msecs at baseline, were twice as likely to have died at 3.7 years follow up. This was supported by Robbins and colleagues (2003) study of 5716 subjects greater than 65 years of age (*HR* = 2.3, 95% C.I. 1.6 – 3.3). Wong's (2003) study of QT interval prolongation in patients post cerebrovascular accident, resulted in a stronger association. They found that a QT interval duration greater than 480 msecs was associated with over three times the risk for death by follow-up (6.3 years), than those with a QT interval duration less than 480 msecs (*HR* = 3.2, 95% C.I. 1.9 – 5.4). Others studies have shown significant but weaker associations. The strength of this relationship

can be attributed to a longer QT interval threshold, longer follow-up, and sicker patient sample.

Sohaib and colleagues (2008) evaluated 3596 men and found that those with QT interval durations greater than 440 ms had one third more risk for mortality than those with a QT interval duration less than 440 msecs (*HR* = 1.33, 95% C.I. 1.11 – 1.59), independent of other variables. Dekker and colleagues (2004) found similar results to Sohaib and colleagues, though failed to reach significance. Salles et al. (2009) study of 538 patients with hypertension reported a slightly higher risk for mortality using a QT interval threshold of 460 msecs (*HR* = 1.68, 95% C.I. 1.09-2.58).

Taken together, an association between QT interval duration and all-cause mortality clearly exists. The degree of this association however is variable, and depends largely upon the QT interval threshold, the population under study, and the time to follow-up. In these studies, the risk for mortality was highest when the thresholds for QT interval prolongation was largest (Wong et al., 2003). The risk for sudden cardiac death with QT interval prolongation has also been evaluated.

Three studies evaluated the association between QT interval prolongation and risk for sudden cardiac death, defined as death with an onset of typical symptoms within 1 or 2 hours, or an un-witnessed or unexplained death. A study by Dekker and colleagues (Dekker et al., 2004) reveals that after 15 years follow up, patients with a QT interval greater than 440 msecs had nearly 4 times the risk for sudden cardiac death than those below 440 msecs (*HR* = 3.7, 95% C.I. 1.3 – 10.9). This study included only elderly men, and excluded women and those with existing cardiac disease.

The larger Rotterdam study (Straus et al., 2006) included both men and women, and excluded only those patients whose electrocardiogram possessed QT interval measurement confounders, e.g. bundle branch block and atrial fibrillation. They found that overall the risk for sudden cardiac death at follow up (6.7 years) was similar between men and women with QT interval prolongation beyond 450 msecs and 470 msecs respectively (men *HR* = 2.6, women *HR* = 2.5). Interestingly, Straus and colleagues found this risk to vary with age, with those with QT interval prolongation aged 55-68 years at 8 times the risk for sudden cardiac death than those with normal QT interval duration at the same age at follow-up. In the group aged over 68 years, the risk for sudden cardiac death at follow-up is reduced (*HR* = 2.1, 95% C.I. 1 – 4.4). This difference in risk could be a result of natural selection. Those who were going to die due to a SCA had already died. This older age group may actually represent individuals who are at low risk for SCA.

The latest study to assess the association between QT interval prolongation and sudden cardiac death was conducted by Chugh and colleagues (Chugh et al., 2009). Though not assessing risk, they found that the odds of sudden cardiac death for those with QT interval prolongation, greater than 450 msecs and 470 msecs for men and women respectively, was more than twice that of those with normal QT interval durations (*OR* = 2.5, 95% C.I. 1.7 – 3.6). In multivariate analysis an interaction was evident. Those with QT interval prolongation without diabetes or QT interval prolonging drugs had over 5 times the odds of sudden cardiac death, than those in other groups. While those with diabetes without QT interval prolonging drugs had twice the odds for sudden cardiac death. A main effect for diabetes and QT interval prolonging drugs was absent. Patients

with a prolonged QT interval, not explained by diabetes or QT interval drugs, were at the highest risk for sudden cardiac death. Together, these studies clearly show an increased risk for sudden cardiac death in patients with QT interval prolongation. This risk though, like prevalence and all-cause mortality, varies.

Studies evaluating the risk for cardiovascular related mortality, in patients with QT interval prolongation, also vary with the population being studied. The majority of studies in relatively healthy populations have found weak associations between QT interval prolongation and risk of death due to a cardiovascular cause (Rautaharju et al., 2006; Robbins et al., 2003; Salles et al., 2009; Sohaib et al., 2008). The greatest risk was shown by Dekker and colleagues (2004), finding that the risk for cardiovascular related mortality by follow-up (3.7 years) for those with QT interval prolongation beyond 440 msecs, was three times that of those with QT interval durations below the established threshold (*HR* = 3.1, 95% C.I. 1.3 – 7.6). This study excluded women and those with prior cardiovascular diseases. It is therefore interesting that they found a significant difference after a relatively short follow-up. Studies in specific disease populations reveal varying rates of risk.

In a hypertensive cohort, Salles and colleagues (2009) show that the risk for cardiovascular related mortality is one and a half times greater for those with a QT interval greater than 460 msecs. In a post cerebrovascular accident sample, the risk for cardiovascular related mortality is much higher, with those with QT intervals above 480 msecs having four times the risk for cardiovascular related mortality than those in the same sample with a QT interval less than 480 msecs (*HR* = 4.1, 95% C.I. 1.7 – 9.8)

(Wong et al., 2003). This threshold is the largest that is used amongst the studies. Expectedly then patients exceeding this threshold have a greater risk for death.

Limitations

The prevalence and risk of adverse outcomes established from QT interval data gathered in these studies should be cautiously evaluated. First, studies collected 12 lead electrocardiograms as part of their study protocol. This data typically represents only 10 seconds of the patient's cardiac function and is subject to considerable intrinsic variability. Second Bazett's correction formula is accepted to cause significant errors, especially with heart rates of high or low extremes (Malik, Hnatkova, & Batchvarov, 2004). Third, the majority of studies used manual or semi-manual methods to measure QT interval data with only 1 or 2 readers. The accuracy of this method though is based largely on these readers competence. Studies have shown that clinician knowledge and competence of QT interval monitoring is poor (Viskin et al., 2005). Finally, the QT interval thresholds were in most studies, arbitrarily established. If this threshold is not established by comparing the distribution across the entire sample, then there is a risk of misclassifying subjects who are not truly QT interval prolonged and therefore not at risk for adverse outcomes. This is evident in Dekker and colleagues study (2004) finding that 35% of subjects have a prolonged QT interval. A study assessing the association between QT interval prolongation and adverse events, using continuous data obtained from a hospital based population, has yet to be conducted.

Conclusion

QT interval prolongation is associated with all cause mortality, sudden cardiac death, and death related to a cardiovascular causes. The prevalence of QT interval prolongation or the magnitude of risk associated with prolongation is dependent upon the methods used for data collection and the population under study. When establishing the risk associated with QT interval prolongation and an adverse event, 10 seconds of data, as obtained from the 12 lead electrocardiogram may be insufficient. In contrast our investigation captures the patient's cardiac rhythm data for their entire length of stay. It is thought that this data, due to its magnitude, will be a better representation of patients' QT interval. Whether QT interval prolongation is related to adverse in-hospital events, is a primary aim of this study.

Measurement Issues in ECG Data Acquisition

No amount of clinician aptitude can ameliorate ECG data that is inadequate. Technical specifications related to the acquisition, process, and analysis of ECG data can facilitate or impede accurate QT interval measurements. These are especially important in continuous automated methods for QT interval monitoring, as the integrity of data acquisition may be impaired over a larger period of time. Consideration of these specifications can improve the quality, reliability and accuracy of QT interval measurements.

Data Acquisition

Proper Acquisition

Accurate QT interval measurement is dependent upon capturing quality ECG signal that is free from noise (artifact). Without noise, the QRS complex onset and T wave end can be easily identified. Three considerations are important to achieve this goal, good skin preparation, a stable body position, and accurate electrode placement.

skin preparation. Good skin preparation will minimize the impedance between the skin and the ECG surface electrode. This can be achieved by removing the patient's chest hair with a disposable razor, soft abrasion to remove the superficial layer of skin (dead skin cells), and the removal of excess skin oils by soap or alcohol (Drew et al., 2004; Pina et al., 1995; Technology, 2006). To improve conductance and hygiene, disposable skin electrodes have been developed and are in wide-use. These electrodes have an inner contact area surrounded by a pre-gelled adhesive to ensure firm contact.

body position. A stable, motionless body position is essential for producing ECG data that is free from extraneous noise. Difficult to filter out, body movement can make an ECG unreadable and mimic diagnostic changes (Drew & Adams, 2001) such as ST elevation or ventricular tachycardia (Adams-Hamoda, Caldwell, Stotts, & Drew, 2003). Patients should be positioned supine and at complete rest (Technology, 2006), minimizing any muscular contractions such as fist tightening or rapid breathing. For continuous monitoring, patient's activities should be relatively minimized. In patients who are experiencing extreme discomfort this may be intolerable and modifications need to be made to ensure patient comfort. If any position changes are needed these should be annotated on the ECG data recording (Technology, 2006).

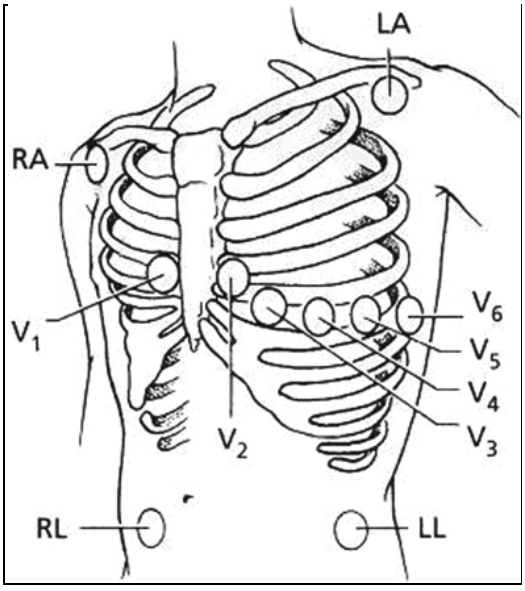
electrode placement. Correct electrode placement is critical for accurate ECG data. Small changes in chest electrode placement will cause waveform changes that can invalidate ECG data. Peripheral electrode changes will also generate inaccurate ECG data (Rudiger, Schöb, & Follath, 2003). In a study of 77 emergency department patients, displacement of chest leads by attending nurses was assessed. Through measuring placement against an established standard, it was found that misplacement of electrodes was common, especially in the lateral leads with older, larger women. Of those participating in the study, approximately 26% of patients' chest leads had a mean displacement greater than 25 millimeters in the horizontal plane and 21 millimeters in the vertical plane (McCann, Holdgate, Mahammad, & Waddington, 2007). This greatly effect's the reliability of the acquired data.

Additionally, electrode placement aptitude of 120 physicians and nurses from 6 hospitals was directly assessed by Rajaganeshan et al. (2008). Participants were asked to

indicate on a diagram the correct positioning of the 6 chest leads required for a 12 lead ECG. The study found that wide inter-individual and inter-group variation existed, with 49% of nurses and 31% of physicians able to correctly identify the correct placement of ECG chest leads (Rajaganeshan et al., 2008). Leads V1 and V2 were most frequently misplaced. Only 16% of cardiologists were able to correctly place the 6 chest electrodes (Rajaganeshan et al., 2008).

Standard electrode placements are well established for 12 lead electrocardiograms. In some situations, standard electrode placements are not practical. First proposed by Mason and Likar (Mason & Likar, 1966) and now commonly practiced (Figure 5), simple adjustments to standard electrode placements, allows patients the use of their limbs without adversely affecting the quality of ECG data. Electrodes are moved from the peripheries and located on the upper and lower torso. This may cause slight

Figure 5. Mason – Likar Electrode Configuration. Reprinted with Permission. *Circulation.2004;110;2721-2746.*©2004, American Heart Association, Inc.



variation to the acquired ECG data (Drew et al., 2004). It has not been directly tested whether QT interval measurements change as a result of peripheral electrode position changes, though I hypothesize that QT interval measurements are not affected, as electrode relocation may affect signal strength (ST changes), but time sequence data (intervals) would remain constant.

Sampling

The hearts' electrical activity is an analog signal (continuous) that needs to be converted to a digital signal (discrete) to enable processing, visualization, and storage. To achieve this a finite number of measurements are made at standard time points (Gregg et al., 2008). Noise is produced as a result of this process. In reproducing an analog signal, finite measures of voltage, determined by the voltage resolution (typically in increments of 5 microvolts (Gregg et al., 2008) are plotted against finite time periods; determined by the number of measurements made per second (sampling rate). The intersections of voltage and time are plotted, producing an ECG tracing.

The digital reconstruction of the analog signal at any point of time is a discrete number. Therefore its ability to replicate the true analog signal is bound by the voltage resolution and the sampling rate. The error that is produced is known as the quantization noise (Gregg et al., 2008). This can affect the precision of the QT interval.

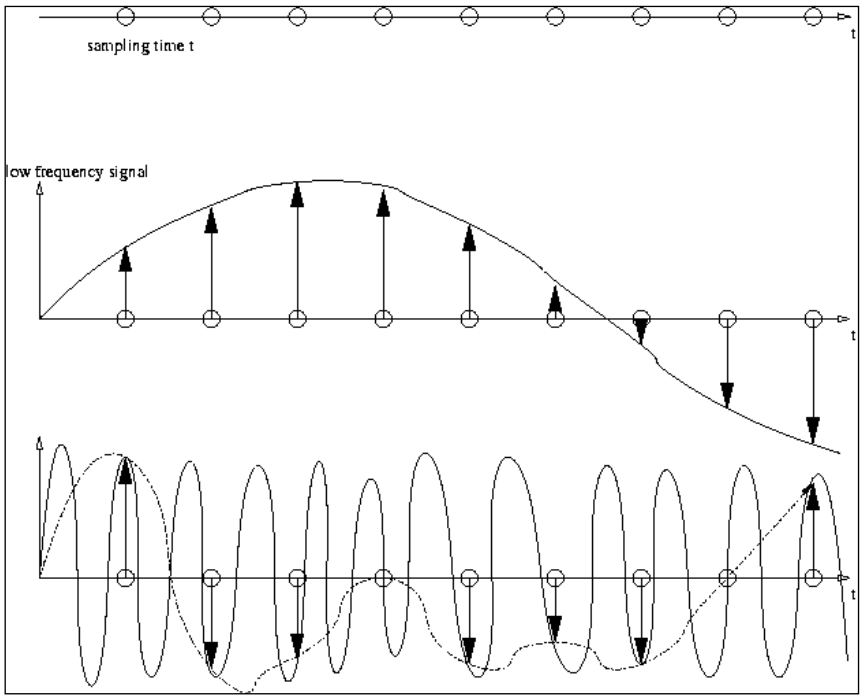
Over sampling

To minimize quantization noise, oversampling is performed. This is based on the Nyquist theorem of sampling; developed by Harry Nyquist in the 1920's (2002). In simple terms the Nyquist theorem states that an analog signal must be sampled at a rate

that is at least twice its signal bandwidth to be able to fully reproduce the original analog signal (Gregg et al., 2008). Clearly, if one wanted to reproduce a curve based on finite samples, the accuracy of this reproduction will be greater if it is based on many samples. This is the basis of oversampling (Figure 6).

Standard 12 lead ECGs are very sensitive sampling between 1000-2000 samples per second; newer technology samples between 10,000-15,000 samples per second (Kligfield et al., 2007). This enables detection of pacemaker spikes with very high frequency.

Figure 6. Example of Nyquist Theory (unknown, n.d)



Minimizing Noise

In addition to quantification noise, the critical care environment has the potential to produce significant artifact affecting the clarity of the ECG data. Ventilators, automated drug delivery devices, intravenous pumps, non-cardiac monitoring equipment, and automated therapeutics such as calf-stimulators, can inadvertently affect ECG data quality. Patient factors such as breathing, eating and movement will also affect the quality of captured ECG data. Controlling for these factors is essential to acquiring accurate ECG data.

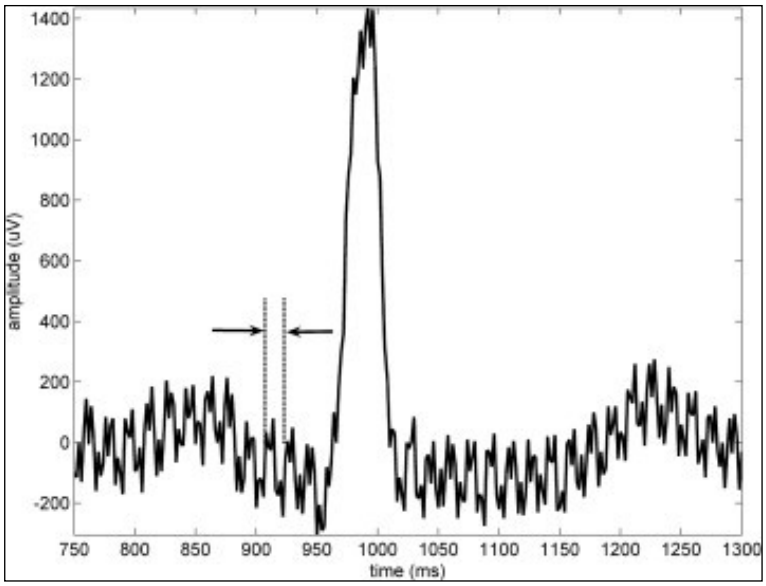
muscle artifact. Muscle movement is initiated by an electrical signal stimulating the myocytes into action, and is a major form of artifact. This signal can be recorded on an ECG and is known as an electromyographic signal (EMG). Often it will appear on the ECG output as high-frequency, narrow, rapid spikes (Chase & Brady, 2000). Depending on the magnitude of movement, these movements can be dangerously rhythmic, mimicking arrhythmias such as ventricular tachycardia, such as with a patient with Parkinson's tremor (Chase & Brady, 2000), or be erratic, resulting in an indistinguishable ECG output. Annotating the presence of tremors on the ECG output allows the interpreter to correctly characterize the waveforms as muscle artifact.

To ensure quality data, steps should be taken to minimize patient movement. In the critical care setting it is practical to administer pain/sedative medications before attempting to gather ECG data. Additionally, fully explaining the ECG procedure to the patient will improve cooperation. Privacy and comfort factors should be considered to

improve patient participation. Many of these considerations are unable to be made within our investigation due to the continuous collection of data.

electrical interference. Depending on the country, electricity is delivered in an alternating current at varying rates measured in Hertz; an indication of cycles per second. Within Canada and the United States, electricity is delivered at 60Hertz. Simply, electrical current is supplied in an alternating direction, 120 times per second, or 60 full cycles. Other countries such as Australia, New Zealand and the United Kingdom, deliver

Figure 7. Example of Common Interference (R. E. Gregg et al., 2008 with permission from Elsevier)

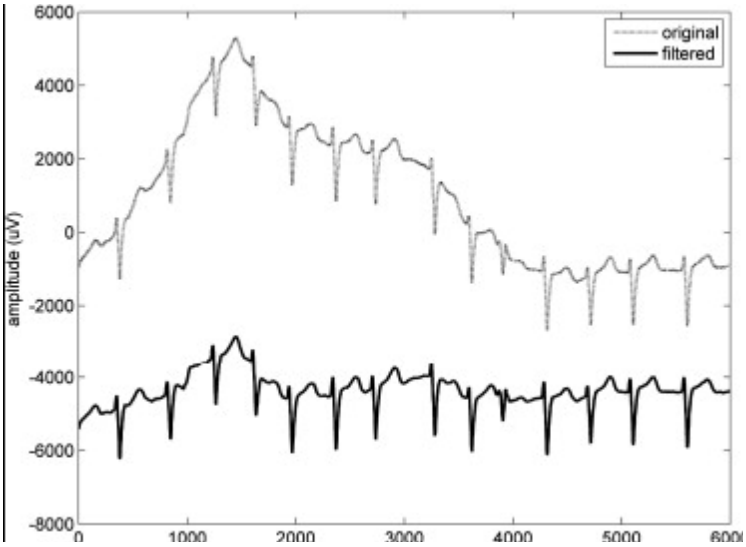


electricity at the slower rate of 50Hertz. Being an electrical signal, the interference produced will display as rapid, high-frequency spikes on the electrocardiogram. These spikes represent one cycle of alternating electrical current and are spaced approximately 17milliseconds apart or 60 spikes per second (Figure 7).

Electrical interference is the main source for what is termed *common-mode-interference* (Gregg et al., 2008). This is interference that is common to all electrodes, when compared to the earth (ground) wire. This interference greatly reduces the interpretability of the electrocardiogram data and needs to be filtered out.

baseline wander. When the heart is mechanically at rest, before and after ventricular contraction, characterized as the PR and TP intervals, the ECG tracing returns to a resting level, termed the baseline. During this time the ECG output is relatively horizontal. However during baseline wander the ECG tracing does not return to the baseline, instead returning to a resting level that is non-uniform, varying vertically (Figure 8). Opposite to high frequency electrical or muscular interference, baseline wander is lower in frequency, often below 0.5 Hertz, and is relatively easier to remove. Baseline wander can be caused by perspiration, movement, or respiration.

Figure 8. Example of Baseline Wander (Gregg, Zhou, Lindauer, Helfenbein, & Giuliano, 2008 with permission from Elsevier)



Data Processing

On the skin's surface the remaining electrical signal produced by the heart is of low amplitude (weak). Furthermore external factors such as muscular movement and respiration can cause considerable noise. This alters the signal-to-noise ratio (Gregg et al., 2008). That is, the level of signal compared to the amount of external noise. A low signal in the presence of high noise needs to be modified to acquire ECG data that is interpretable. To do this, three techniques are commonly used: 1) right-leg drive, 2) bandwidth filtering, and 3) signal amplification

common-mode-interference. One of the first ways the ECG minimizes noise is to cancel out common-mode-interference. This is electrical interference that is present in multiple leads. This is measured and subtracted from each lead. The remaining difference between leads is considered the true signal (Gregg et al., 2008) which is then recorded. However each electrode does not experience the exact amount of common-mode-interference. Therefore an additional method for subtracting out interference is needed.

right leg drive. Right leg drive is used as a method to actively cancel out remaining common-mode-interference. Not all electrodes will experience interference in the same magnitude. Therefore a small signal is sent to the right leg, opposing the interfering signal. This continues until the common-mode-interference signal is canceled, or approaches zero (Gregg et al., 2008).

filtering. Once common-mode-interference is reduced, analog filters are used to attenuate (reduce) unwanted, uncommon high frequency signals, such as muscle artifact,

and low frequency signals, such as respiration. The needs of the ECG data will dictate the thresholds of filters that are applied.

low-frequency filter. Heart rate per second determines the lowest bound frequency that is included in an electrocardiogram. For example, a patient with a heart rate of 30 beats per minute has 1 heartbeat (cycle) every 2 seconds, or simply 0.5 cycles per second; this is equivalent to saying 0.5Hertz. Therefore the lowest bound frequency of information that is desirable to be collected is 0.5Hertz. In clinical practice low-frequency filters are set between 0.05Hertz and 0.67Hertz (Gregg et al., 2008).

When a low-frequency (high-pass) filter is applied, only frequencies greater than the minimal bound are acquired. For example, respiration is considered to occur below 20 cycles per minute or 0.33Hertz. Therefore with a 0.5Hertz filter, the respiration signal is attenuated. One criticism of a low-frequency filtering is that it will distort low frequency signals, such as the ST-segment. To correct for this, a linear-bidirectional high-pass filter can be applied. The negative to this is the loss of real-time processing (Gregg et al., 2008; Kligfield et al., 2007) as it needs to be performed in both forward and backward directions.

high-frequency filter. Opposite to the low-frequency filter, the high-frequency (low-pass) filter attenuates signals that are above a specified signal frequency. Minimum standard for diagnostic ECG is 150Hertz, however for continuous monitoring or with extraneous noise, such as that experienced by acute care patients in emergency departments, a high-frequency filter can be set as low as 40Hertz. This will attenuate

higher frequency signals, resulting in loss of waveform amplitudes. Therefore this filter should not be used when a diagnostic electrocardiogram is needed (Gregg et al., 2008).

Amplification. Once the analog ECG data has been acquired and appropriately filtered, the remaining signal is amplified by a gain of 1000 (Gregg et al., 2008) and converted from analog to a digital signal. The digital signal is then ready for analysis.

Data Analysis

Once signal acquisition and processing has been completed, diagnostic algorithms are applied to the digital signal. The performance of these algorithms varies however, depending on the type of data that they are applied to: diagnostic 12 lead ECG data versus continuous ambulatory data. Diagnostic 12 lead ECG analysis is based on 12 leads of data that is commonly acquired with a sample rate of 500 samples per second and a bandwidth of approximately 0.05Hertz-150Hertz (Gregg et al., 2007). Whereas continuous ambulatory data is recorded in a subset of leads, with high-frequency, low pass filtering at 40Hertz and sampled at the lesser rate of 200 samples per second (Gregg et al., 2007). The resolution and reproducibility of the acquired signal from continuous ambulatory data, is greatly reduced. This is a dilemma for staff nurses when comparing QT interval measurements derived from different methods.

Twelve lead ECGs provide a closer approximation of the original analog signal, but is not congruent with sound QT interval monitoring practices. The QT interval varies over time in response to noxious stimuli. Therefore a 10-second ECG needs to be completed at the time of maximal effect, without error, to adequately characterize the patients' repolarization changes: a difficult task in the clinical setting. Currently QT

interval measurements are performed haphazardly on single, random, QRST complexes, in one lead (Helfenbein et al., 2006). With considerable inter-individual and beat-to-beat variation and an inability for clinicians to correctly calculate the QT interval, current QT interval monitoring practices, despite using high resolution data, often are not accurate.

In an effort to improve the accuracy and reliability of QT interval measurements in the clinical setting, automated methods have been designed for use with lower resolution, continuous ambulatory data. These methods are similar to what is currently available in standard ECG technology. Unique challenges exist however as continuous ambulatory monitoring data is gained from a subset of leads, has considerable motion and muscle artifact/noise, more opportunity for environmental and electrical interferences, and due to its real time nature, less time for analysis.

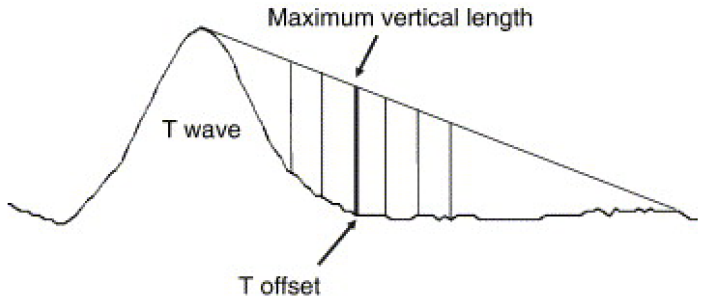
continuous QT interval monitoring. To improve reliability and accuracy our investigation utilizes a new proprietary continuous QT interval monitoring system. A description of the stability attained with this system is provided below (Helfenbein et al., 2006).

- *Providing real-time data:* QRS complexes are characterized and normal atrial paced beats are clustered and matched for similarity. Similarly characterized beats are then averaged to form a representative complex for each lead.
- *Minimizing noise and motion artifact*: 15 second periods of data are clustered and outlying values are removed by median beat selection within each period. Baseline wander is reduced by subtracting an isoelectric point to a point of

reference, before each QRS complex. All available leads are then combined to form one root-mean-square (RMS) (vector) ECG signal.

- *Minimizing variability:* The RMS wave is made by summing the square of each representative complex from all available leads, divided by the number of leads. A square root function is then performed. If the T wave amplitude in the RMS wave is greater than a pre-defined threshold, the Q onset and T wave offset are measured.
- *Reliability of measurement:* A line segment is drawn from the T wave peak, to a heart-rate adjusted point on the baseline to establish the T wave end. The longest vertical distance is considered to be the T wave end point (Figure 9).

Figure 9. Proprietary Method for Identification of T wave End (Helfenbein et al., 2006 with permission from Elsevier)



- The QT interval is calculated using a Fridericia correction formula and a median filtered heart rate from the 15 second period. This establishes a raw QTc interval.
- The final QT interval is obtained by median filtering the 13 previous 15-second periods.

The benefits of these methods for data analysis are numerous. 1) By using an RMS wave, information from each lead is combined. Therefore, if one lead has a clear QRS onset yet an unclear T wave end, or conversely an unclear QRS onset and clear T wave end, an accurate QT interval measurement will still be achievable. 2) The method for determining the T wave end reduces measurement error associated with manual measurements. 3) Variations resulting from noise such as that produced by position changes or electrode-measurement issues, will not negate QT interval measurements, and finally, 4) median filtering reduces variability by removing outliers and providing stable measurements.

Besides the benefits of this method for data analysis, some negatives exist when compared to the diagnostic 12 lead electrocardiogram. 1) Bedside cardiac monitoring data is of lesser quality due to a lower sample rate and resolution. This is necessary to record, analyze and record rhythm data prospectively, on a continuous basis. Therefore measurement error exists. 2) Although measurement is from all available leads, continuous ambulatory data is recorded with fewer leads, also 3) significant external noise exists in the ambulatory setting, further increasing the potential for measurement errors. To account for this, patients identified as having QT interval prolongation were manually over read. This is described further in the methods.

Summary

Quality cardiac rhythm data requires nurses to be considerate in preparing patients for cardiac monitoring. Proper skin preparation, electrode placement, and body position is essential to minimize noise such as that produced by muscle movement, electrical interference and baseline wander. Technically these can be modified by common-mode-

interference minimization, right leg drive filtering, and high and low pass filters. The continuous QT interval monitoring system is designed to be very stable against these types of extraneous noise. This will be the first study that has utilized this technology. The study's methodology is described next.

CHAPTER 3

METHODS

Study Design

This study consists of two separate but related investigations. The first investigation is a quasi-experimental study using a pre test post test design with a purposive cohort of registered nurses, aimed at evaluating the ability of nurses to perform QT interval monitoring. This was conducted in November and December, 2007. The second investigation is a prospective observational study of a cohort of patients admitted to a hospital unit receiving cardiac monitoring. This investigation was conducted during a 2 month period between October and December, 2008, and aims to establish the need for QT interval monitoring, the prevalence and predictors of QT interval prolongation, and the association to adverse in-hospital events.

Ethics

The study was approved by the University of California San Francisco's Committee on Human Research (H6052-29981), the Institutional Review Board of Stanford University (protocol #7967), and Stanford University Medical Center's Nursing Research Council.

Setting

This study was conducted with nurses and patients from all adult in-patient units providing continuous cardiac monitoring at Stanford University Medical Center (SUMC), a large academic level 1 trauma center, licensed for 594 beds. In all, data from 146

patient beds and 391 nurses across 5 inpatient units were included in this study. Description of each participating unit is provided (Table 6).

Table 6. Description of Participating Hospital Units

Abbreviation	Type	# Beds	# Nurses
CICU	Cardiovascular Intensive Care Unit	25	117
MST	Medical/Surgical/Trauma Intensive Care Unit	33	152
CCU	Coronary Care & Cardiac Surveillance Unit	22	71
CIICU	Cardiology Intermediate Intensive Care Unit	26	51
MSTI	Medical/Surgical/Trauma Intermediate I.C.U.	40	91

Sample

nurse. All nurses employed in an inpatient unit providing continuous cardiac monitoring were invited to participate in the quasi-experimental pre test post test investigation of nurses' QT interval related knowledge and abilities. Nurses were paid their hourly salary to attend the class. Funding was provided by Philips Medical Systems through a restricted educational grant. The content of the class was determined by the research team. Philips Medical Systems had no input or oversight of the content. Written consent was obtained by all participating nurses. Those who did not provided written consent were excluded from the study.

To increase nurse participation, nursing administration were sought to identify barriers to attendance. In response to feedback, education classes were scheduled throughout the day and night (up to 2 am). In addition, recruitment flyers were posted in conspicuous places and email notifications sent out through the units' list-serve. In total 391/482 nurses attended 1 of 44 education classes provided.

patient. Data from all patients admitted to a study unit during the 2 month investigation period were collected. As there was no patient contact and usual care was provided, a waiver of consent was approved by regulating ethics bodies. No patients were excluded during data collection. During data analysis for QT interval prolongation, patients with electrocardiographic confounders to QT interval length were excluded. These are detailed further on.

Instruments

nurses. The QT interval knowledge test (Appendix A) is a 13-question researcher developed tool based on the AHA practice standards related to QT interval monitoring (Drew et al., 2004). This is a modified version of the one used in the pilot study (Pickham & Drew, 2007). Content validity was established with expert consultation.

The knowledge test consisted of 8 fixed response questions, 2 skill based questions, 2 measurement questions, and a single question asking nurses to calculate the QTc interval. Items were assigned the value of 1 for a correct answer. The maximal score achievable on this instrument was 13. Although Bazett's heart rate correction formula was demonstrated within the education class, any valid published QT interval correction formula was accepted for calculation of the QTc interval. A generous margin of error (40 milliseconds) was used for categorizing a correct response for questions requiring measurement or calculation. All knowledge tests were scored by the researcher.

patients. Proprietary continuous QT interval monitoring software (Helfenbein et al., 2006) was installed into the pre-existing Philips Intellivue Patient Monitoring System (Revision K & Revision J, Philips Medical Systems). The function of the continuous QT

interval algorithm has been detailed previously. Briefly, the continuous QT interval monitoring system uses all available monitoring leads, 3 limb leads, 3 augmented leads, and 1 chest lead, to construct an averaged waveform. The proprietary algorithm uses this constructed waveform and an averaged heart rate to continually calculate the QTc interval in real time.

Data Collection Methods

nurses. Nursing leadership at SUMC were implementing the AHA practice standards (Drew et al., 2004) as part of a nurse-led evidenced based practice initiative. As part of this implementation we designed a 1 hour QT interval intensive education intervention. As this was a practice initiative, all nurses employed on a unit providing continuous cardiac monitoring (n = 480) were required to attend.

At the beginning of each class, nurses completed the QT interval knowledge test. The pretest allowed subjects to self evaluate their current QT interval related knowledge. At this time nurses were provided an information flyer informing them of the study and a consent form. After completion of the pretest a QT interval intensive education class was provided. This class reviewed the AHA practice standards as they relate to QT interval monitoring, demonstrated how to measure the QT interval, reviewed common proarrhythmic drugs, electrocardiographic signs of impending TdP, and concluded with case study examples. A short question and answer period followed allowing for clarification of presented material. At completion, nurses wishing to participate in the study provided signed consent and were given the same QT-related knowledge test to complete. Non-consenting nurses were excused and their pre test was not collected.

Nominal identification numbers were used to match nurses' pre and post tests for analyses. Stationary supplies and calculators were provided.

patients. Continuous QT interval data. As part of usual care patients were provided continuous cardiac monitoring during their admittance to a study unit. Continuous QT interval monitoring software was installed and defaulted *on* for all patient beds (Philips Intellivue Patient Monitoring System, Philips Medical Systems). This minimized the impact on nursing care and standardized QT interval monitoring for all study units. Rhythm data were transmitted from the bedside to an off-unit, on-site, dedicated personal computer every 8 hours (Research Data Export, Philips Medical Systems). This was collected and stored on external media by researchers for analyses. As standard practice patients Medical Record Numbers (MRN) were entered into the Philips Intellivue Patient Monitoring System to act as a unique patient identifier. These were nominally re-coded into unique study identification numbers and all patient identifiers within the rhythm data were electronically removed. Patients who were re-admitted or transferred during the investigation period were consolidated under a sole study identification number.

Clinical data. Relevant clinical data were abstracted verbatim from the medical record. Initial measurements were used for systolic blood pressure, diastolic blood pressure, body surface area, weight in kilograms, and automated 12 lead electrocardiogram variables. Lowest serum level obtained during the investigation was used for potassium, sodium, chloride, calcium, magnesium, and highest serum level recorded for glucose, creatinine, and blood urea nitrogen. Results for creatinine and blood urea nitrogen were abstracted from the same sample report. Any serum value within the

monitoring period was recorded for thyroid stimulating hormone (TSH). Operational definitions for data are provided (Appendix B). Drugs with a known proarrhythmic affect (Woosley, 2004) were obtained from patients' medication administration record (MAR). Admission reports were obtained from the emergency department for admission diagnoses of intentional drug overdose.

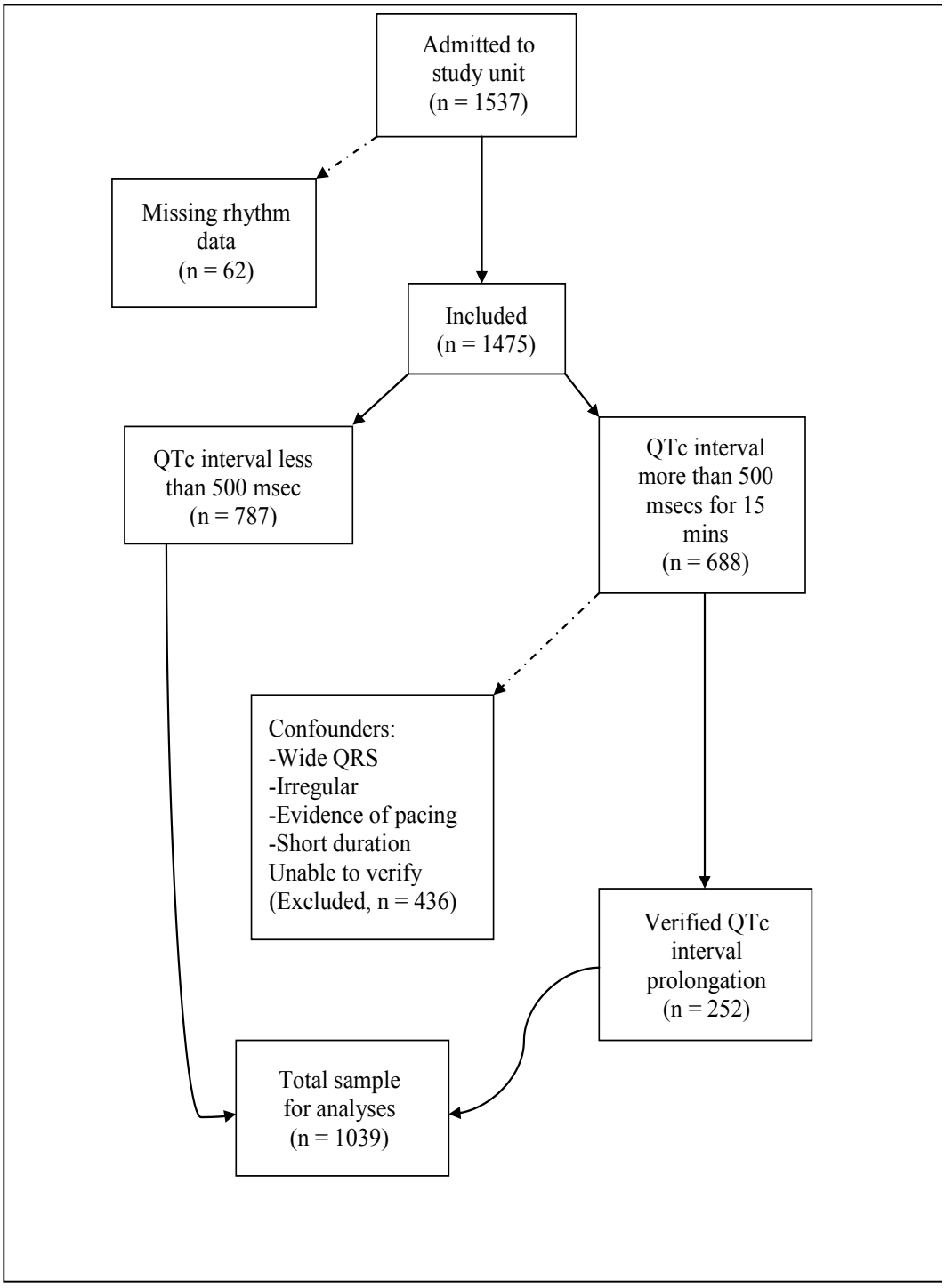
Adverse outcomes data. Adverse in-hospital outcomes were defined as 1) death due to all-causes, 2) length of cardiac monitoring and hospitalization, 3) critical intervention from rapid response or code blue team, and 4) electrophysiology laboratory procedure (pacemaker implantation, implantable cardiac defibrillator (ICD) implantation, or ventricular tachycardia ablation) during investigation period. These data were obtained from the medical record, electrophysiology laboratory report, and code blue rapid response data.

Procedures

Determining QT interval prolongation. An algorithm was developed to determine QT interval prolongation for the purpose of this investigation (Figure 10). Patients' QT interval data obtained from the Philips Intellivue Patient Monitoring System was sorted by maximum mean QT interval. Patients with mean QT interval values greater than 500 msecs were identified. On review, those who did not have greater than 15 minutes of QT interval monitoring data or had episodes of QT interval prolongation that were not 15 minutes or longer, were immediately excluded. Using visualization software (Medical Oscilloscope Windows, Philips Medical Systems) the patient's rhythm at the time of QT interval prolongation was manually over-read. Subjects with confounders to QT interval

measurement were excluded: evidence of atrial or ventricular pacing, wide QRS complexes, irregular rhythms, or noisy signal. Of those remaining, automated determinations for Q wave onset and T wave offset were verified for accuracy. Those with inaccurate automated determinations were discarded. The remaining patient's QT interval measures were verified using virtual calipers. Patients were excluded if the researcher could not verify accuracy of measurement using on screen calipers. Patients with a verified QTc interval greater than 500 msecs for 15 minutes or longer were classified as having QT interval prolongation for the purpose of this investigation. It is important to note that as the continuous QT interval monitoring system uses a RMS wave formed from all available leads, manual over read in a single lead will not have complete agreement. Therefore for the purpose of this investigation, if the measurement provided by the continuous QT interval monitoring system was made in a stable rhythm, free of confounders, with an accurate Q wave onset and T wave offset, and the manual over read closely approximated the continuous QT interval measure, it was considered accurate.

Figure 10. Algorithm for Determining QT Interval Prolongation



* The Research Data Export software was unable to export patient rhythm or export file corrupted.

Statistical analysis

SPSS for Windows Graduate Student Version (Release 15.01.1.1) was used for statistical analyses. A value of $p < .05$ was used as a critical value for determining significance. When appropriate, post-hoc analysis was performed with a Bonferroni correction. All sample size calculations were performed using G*Power 3.1.0 (Faul, Erddelder, Lang, & Buchner, 2007). Statistical analyses for each hypothesis were:

Research Question 1. Does a QT interval intensive education class improve nurses' QT interval related knowledge?

Descriptive statistics were used to characterize demographic data: age, sex, years of nursing experience, hospital unit of employment, level of education, and possession of specialty critical care certification. Proportions of correct responses were established for each item. McNemar's test of correlated proportions was used to evaluate for a difference between pre and post knowledge tests. A paired samples Students t-test was used for continuous data. An analysis of variance (ANOVA) was used to evaluate for differences in total test scores and nurse's hospital unit of employment, years of nursing experience, level of education, and possession of specialty certification.

Sample size calculation: The number of nurses needed to identify a moderate effect ($r = .5$) with an alpha (α) probability of .01 and a power probability of .80 was 51.

Research Question 2. What proportion of patients admitted to a study unit, have an AHA indication for QT interval monitoring?

Patients with an episode of a heart rate less than 40 beats per minute, admitted for treatment after an overdose of a drug, were administered a proarrhythmic drug, or had low serum potassium or magnesium levels, were identified and coded into dichotomous variables. Simple frequencies were used to determine the number of AHA indications per patient. An overall proportion of those with at least one AHA indication was determined.

Research Question 3. Are the AHA indications for QT interval monitoring effective in identifying patients that at are at risk for developing QT interval prolongation while admitted to a unit providing continuous cardiac monitoring?

Patients were dichotomized for both QT interval status (non-prolonged, prolonged) and presence of AHA indication for QT interval monitoring. A 2 x 2 contingency table was used to determine if there was a relationship between AHA indications for QT interval monitoring and QT interval prolongation. A Fisher's exact p value was evaluated for significance.

Sample size calculation: The expected proportion of QT interval prolongation in those without AHA indications (P1) was .05. The expected proportion of QT interval prolongation in patients with AHA indications (P2) was .20. As we expected more patients to have AHA indications for QT interval monitoring, an allocation ratio of 2 was used. To determine a significant relationship between these groups using an alpha (α) probability of .05 and a power probability of .80, 52 patients were needed without AHA

indications and 104 were needed with AHA indications. The total sample size needed was 156.

Research Question 4. What are the demographic and clinical variables that contribute to a model that best predicts those patients admitted to a unit providing continuous cardiac monitoring who experience QT interval prolongation?

Patients were dichotomized according to their QT interval status (non-prolonged, prolonged). This was used as the dependent variable. Univariate analyses testing the dependent variable against demographic and clinical variables, was performed using appropriate tests (e.g. Students t test, ANOVA, Pearson's correlation, Chi square). Significant independent variables ($p < .20$) were selected for entry into a multivariate logistic regression. As differences in QT interval length are known to exist between sexes and various age groups, these variables remained in the model regardless of the level of significance. Non-significant variables were removed from the model one-by-one based on the lowest level of significance (highest *p* value) and the model was re-run. This continued until only significant variables remained in the model.

Research Question 5. Is QT interval prolongation associated with a) all-cause in-hospital mortality, b) increased length of hospitalization and cardiac monitoring time, c) critical intervention (code blue, medical rapid response), and d) device intervention (pacemaker, interval cardiac defibrillator).

Mortality. All-cause in-hospital mortality was dichotomized to a dependent variable. A 2 x 2 contingency table was used to determine if a relationship existed between QT interval prolongation and all-cause mortality. A Fisher's exact test p value

was evaluated for significance. To assess if QT interval prolongation predicted all-cause in-hospital mortality a binary logistic regression was performed using the same methodology as in research question #4. The model was complete when only significant variables remained. Age and sex remained in the model regardless of level of significance.

Sample size calculation: The expected proportion of QT interval prolongation in those alive at discharge (P1) was .20. The expected proportion of QT interval prolongation in the mortality group (P2) was estimated to be .50. As we expected more patients to be alive at discharge, an allocation ratio of .05 is used for the mortality group. To determine a significant relationship between these groups using an alpha (α) probability of .05 and a power probability of .80, 352 patients were needed in the alive at discharge group and 18 patients were needed in the mortality group. The total sample size needed was 371. If the proportion of QT interval prolongation in those with all-cause mortality was lower (P2 = .30), then 129 patients were needed in the mortality group and 2570 patients were needed in the alive on discharge group. Total number of patients needed would be 2699.

Length of QT interval monitoring. QT interval data were generated each minute from the Philips Intellivue Monitoring System. The number of measurements made can be used as a proxy for total cardiac monitoring time. Descriptive statistics were used to characterize these data. A Student's t test was used to assess for differences between those with QT interval prolongation and those without.

Sample size calculation: The number of patients needed to identify a moderate difference ($r = .5$) with an alpha (α) probability of .05 and a power probability of .80 was 51 patients per group. The total number of patients needed was 102. If the effect size was smaller ($r = .2$), 310 patients would be needed in each group, for a total sample of 620 patients.

Length of admission. A date variable was established from admission and discharge data. Descriptive statistics were used to characterize these data. A Student's t test was used to assess for a difference between those with QT interval prolongation and those without. To assess if QT interval prolongation was an independent predictor for length of hospitalization a multivariate linear regression was used. Significant variables at the $p < .2$ level with univariate analysis, were entered into a multivariate model. Sex and age were adjusted for regardless of level of significance.

Sample size calculation: The number of patients needed to identify a moderate difference ($r = .5$) with an alpha (α) probability of .05 and a power probability of .80 was 51 patients per group. The total number of patients needed was 102. If the effect size was smaller ($r = .2$), 310 patients would be needed in each group, for a total sample of 620 patients.

For multiple linear regression with 10 predictors, an alpha probability of .05 and power probability of .80 would be able to detect a moderate effect size ($f^2 = .15$), using a total sample size of 118 patients. If the effect size was small ($f^2 = .02$), 822 subjects would be needed.

Critical interventions. Rapid response and code blue team response data were dichotomized into a dependent variable. A 2 x 2 contingency table was used to determine if a relationship existed between critical intervention and QT interval prolongation. A Fisher's exact test *p* value was assessed for significance. To determine if QT interval prolongation was an independent predictor for needing critical intervention, a binary logistic regression was performed. Similar methodology as that used in research #4 was used. A complete model was found when only significant variables remained. Age and sex were adjusted for regardless of their level of significance.

Sample size calculation: The expected proportion of QT interval prolongation in those without critical intervention (P1) was .20. The expected proportion of QT interval prolongation in patients needing critical intervention (P2) was estimated to be .50. As we expected more patients to not need critical intervention, an allocation ratio of .05 was used for the critical intervention group. To determine a significant relationship between these groups using an alpha (α) probability of .05 and a power probability of .80, 18 patients were needed in the critical intervention group and 353 patients were needed in the group not requiring critical intervention. The total sample size needed was 371.

Device interventions. Electrophysiology laboratory procedures were dichotomized into a dependent variable. A 2 x 2 contingency table was to determine if a relationship existed between device intervention and QT interval prolongation. A Fisher's exact test *p* value was assessed for significance.

Sample size calculation: The expected proportion of QT interval prolongation in those without device intervention (P1) was .20. The expected proportion of QT interval

prolongation in patients needing device intervention (P2) was estimated to be .50. As we expected more patients to not need device intervention, an allocation ratio of .05 was used for the device intervention group. To determine a significant relationship between these groups using an alpha (α) probability of .05 and a power probability of .80, 18 patients were needed in the device intervention group and 353 patients were needed in the group not requiring device intervention. The total sample size needed was 371.

CHAPTER 4

RESULTS

Nurses Investigation

Sample

A total of 391 nurses (81.1%) participated in the education investigation. Sample characteristics are shown (Table 7). Participating nurses were predominately women (83.9%), possessed a Bachelor's degree level of education or higher (77.3%), and had greater than 5 years of nursing experience (70.8%). 379 nurses completed both the pre test and post test.

Table 7. Demographics of Nursing Sample (n = 391)

Age	
- Mean	39.25 (*SD* 10.1)
- Range	22 – 70
Missing	(n = 5, 1.3 %)
Sex	
- Women	328 (83.9 %)
- Men	52 (13.3 %)
Missing	(n = 11, 2.8 %)
Hospital Unit	
- CICU	100 (25.6%)
- MST	82 (21.0 %)
- CCU	68 (17.4 %)
- CIICU	43 (11.0 %)
- MSTI	94 (24.0 %)
Missing	(n = 4, 1.0 %)
Nursing Experience	
- < 1 year	20 (5.1 %)
- 1 – 2.9 years	42 (10.7 %)
- 3 – 4.9 years	49 (12.5 %)
- 5 – 9.9 years	85 (21.7 %)
- 10 – 14.9 years	64 (16.4 %)
- > 15 years	128 (32.7 %)
Missing	(n = 3, 1.0 %)
Level of Education	
- Diploma	8 (2.0 %)
- Associates degree	70 (17.9 %)
- Bachelor degree	270 (69.1 %)
- Masters degree	32 (8.2 %)
- Doctoral degree	0 (0.0 %)
Missing	(n = 11, 2.8 %)
Possession of specialty certification	
- Critical Care Nurse (CCRN)	56 (14.3 %)
- Other	13 (3.3 %)
- None	322 (82.4 %)

Research Question 1. Does a QT interval intensive education class improve nurses' QT interval related knowledge?

Four hundred and eight nurses participated in the QT interval intensive education class; 391 provided consent to participate in the study (95.8%). In all 379 nurses completed both the pre test and post test. A copy of the instrument used to assess QT interval related knowledge is provided (Appendix A). The maximum score achievable was 13.

The proportions of correct responses for each item are shown (Table 8). The proportion of correct responses significantly increased after education for all items assessing nurse's knowledge of the AHA recommendations. Nurse's skills and abilities also improved. At baseline 64.8% of nurses correctly marked the QT interval on a sample rhythm strip and 46.5% correctly measured the QT interval. Only 5.6% of nurses correctly calculated the QTc interval. After the education intervention the proportion of correct responses increased significantly; 90.0% of nurses correctly marked the QT interval, 84.1% correctly measured the QT interval and 51.9% correctly calculated the QTc interval. Total test scores also increased significantly from pre test (M = 5.76, SD 2.33) to post test (M = 9.98, SD 2.07), by a mean increase of 4 correct responses (M = 4.22, SD 2.57, *95% C.I.* 3.96 – 4.48, $p < .0005$).

Table 8. Proportion of Correct Knowledge Test Items

Question	Pre %	Post %	*p*
Knowledge of AHA recommendations			
QT interval prolongation increases risk for TdP	59.6	99.0	< .0005
Of the choices, monomorphic VT is not a sign for TdP	27.9	70.1	< .0005
CLQTS, long pauses, SAH, can cause QT prolongation	35.5	70.3	< .0005
AHA states QT should be monitored q8 hours or more	88.5	98.2	< .0005
QTc interval = QT if HR were 60 bpm	35.0	92.3	< .0005
Overdose is priority for monitoring	58.9	90.3	< .0005
Bundle branch block artificially prolongs QT interval	55.0	77.7	< .0005
Risk for TdP greatest with Ibutilide after long pause	28.9	58.3	< .0005
QT interval monitoring ability			
Mark the QT interval on rhythm strip	64.8	90.7	< .0005
Mark the RR interval on rhythm strip	83.2	90.0	.024
Measure the QT interval	46.5	84.1	< .0005
Measure the RR interval	34.5	70.8	< .0005
Calculate QTc interval	5.6	51.9	< .0005

To evaluate for differences in mean total test score between hospital units, an analysis of variance (ANOVA) was performed. On pre test, mean total test scores varied significantly among hospital units (Table 9) (F = 14.376, df 4,371, p < .0005), with CCU performing better than all other units (M = 7.48, SD 2.0). After the education intervention, differences among the groups remained (F = 5.385, df 4,371, p < .0005), but nurses from MST performed best (M = 10.55, SD = 2.0). In post hoc analyses, nurses from MST performed significantly better than nurses from CICU and CIICU, but equally to nurses from CCU and MSTI.

Pre test mean total test scores also varied significantly among nurses with different levels of education (F= 6.929, df 3,367 p < .0005). Nurses with a Masters level of nursing education performed best (M = 7.42, SD 2.5); all other education groups were

equal. On post test however this difference no longer existed (F = 1.31, df 3,375, p = .272), all groups were equal.

Table 9. Mean Total Test Scores by Hospital Unit.

Unit	Pre	Post
CICU	5.04 (2.1)	9.57 (2.1)
MST	5.50 (2.4)	10.55 (2.0)
CCU	7.48 (2.0)	10.31 (2.1)
CIICU	5.88 (2.1)	9.14 (2.1)
MSTI	5.31 (2.1)	10.13 (2.0)

On years of nursing experience pre test and post test mean total test scores did not vary significantly (F = 1.365, df 5,373, p = .237, & F = 0.551, df 5,381, p = .737 respectively) (Table 10), or by possession of specialty certificate (F = 2.54, df 1,66, p = .116, & F = 0.196, df 1,67, p = .659 respectively). Taken together, after a one hour education intervention nurses performed significantly better on all elements of an instrument designed to assess their QT interval related knowledge and skills.

Table 10. Mean Total Test Score by Years of Nurses' Experience

Years of Experience	Pre	Post
< 1 year	6.15 (2.1)	9.75 (2.2)
1 – 2.9 years	5.93 (2.5)	10.10 (2.1)
3 – 4.9 years	5.19 (2.3)	10.20 (2.1)
5 – 9.9 years	5.55 (2.4)	10.14 (2.2)
10 – 14.9 years	6.22 (2.1)	10.08 (1.8)
>15 years	5.78 (2.4)	9.78 (2.1)

Patient Investigation

Sample

There were 1537 patients admitted to a hospital unit providing cardiac monitoring during the 2 month investigation period. Of these 1039 patients remained after exclusions (see methods). Sample characteristics are shown (Table 11). The sample consisted of more men than women (54% v 46%), were predominately white (64%), and older (*M* = 60.15 years, *SD* = 18.65). The racial composition was reflective of the San Francisco bay area community (i.e. 64% White, 12% Asian, 6% Black, 14% Hispanic, & 4% other).

Table 11. Characteristics of Patient Sample.

Age (n = 1039)	
- Mean (years)	60.15 (18.65)
- Range (years)	85 (15 – 100)
Sex	
- Women	478 (46 %)
- Men	561 (54 %)
Race	
- White	662 (63.7 %)
- Asian	130 (12.5 %)
- Black	62 (6.0 %)
- Hispanic	147 (14.1 %)
- Other	38 (3.7 %)
Hospital Unit	
- CICU	137 (13.3 %)
- MST	282 (27.4 %)
- CCU	105 (10.2 %)
- CIICU	299 (28.8 %)
- MSTI	207 (19.9 %)
Missing	(n = 9, 0.9 %)

QT interval monitoring data

Over the two month investigation, an average of 65.14 hours of continuous monitoring data were collected from each patient (*SD* = 115.12, *median* 32.3 hrs, *range* 0.26 hrs – 1464 hrs). In total 67648.23 hours of continuous QT interval data were collected. Mean QT interval monitoring time did not differ between men and women (65.97 v 64.18 hrs, $p = .77$).

QT interval duration

The overall Fridericia corrected averaged-mean QT interval was 431.70 msecs (*SD* = 28.10, *IQR* 413.27 msecs – 448.26 msecs, *95% C.I.* 390.47 - 476.35). Averaged-mean QT interval duration differed by sex, with women's averaged-mean QT interval (435.87 msec) significantly greater than that of men (428.14 msecs) ($t = 4.463$, *df 1037*, $p < .0005$), by an average of 7.7 msecs (*95% C.I.* 4.3 – 11.1). These differences were expected. Upper 5% values also differed between sexes (women 479.77 msec, men = 474.21 msec); these were not tested for significance. Averaged-mean QT interval duration also differed between age groups (*Welch F* = 15.671, *df* 3, $p < .0005$) (Table 12). Patients 65 years and older possessed significantly longer averaged-mean QT intervals than those aged 18 – 39 years and 40 – 49 years, but not patients aged 50 – 64

Table 12. Mean QT Interval Duration by Age Group

Age	**n**	**Mean QTc (*SD*)**
18 – 39 years	154	419.92 (24.09)
40 – 49 years	133	424.28 (25.46)
50 – 64 years	314	433.73 (29.02)
65 years >	448	435.81 (29.72)

years. There was no difference in averaged-mean QT interval among racial groups (*Welch F* = 0.876, *df* 4, *p* = .480) (Table 13). This is consistent with prior studies.

Table 13. Mean QT Interval by Race Group

Race	n	Mean QTc (*SD*)
White	668	431.63 (27.23)
Hispanic	149	431.68 (35.61)
Asian	132	430.89 (32.15)
Black	62	426.97 (21.80)
Other	38	435.13 (24.10)

Research Question 2. What proportion of patients admitted to a study unit, have an AHA indication for QT interval monitoring?

Table 14. Proportions of Patients with AHA Indications

Indication	Men n = 847		Women n = 690			Overall N = 1537	
	n	%	n	%	*p*	n	%
Overdose admission	0	0.0	1	0.1	-	1	0.1
Proarrhythmic drug administration	501	59.1	449	65.1	.018	950	61.8
Episode of HR below 40 bpm	42	4.8	35	5.5	.907	77	5.2
Serum potassium (<3.5 mEq/L)	250	30.5	268	39.7	< .0005	518	34.6
Serum magnesium (<1.5mEq/L)	77	9.1	100	14.5	.001	177	11.5

The rarest indication for QT interval monitoring was admission after drug overdose (Table 14). This was followed by bradycardia and low serum magnesium and low serum potassium. Administration of a proarrhythmic drug was the most commonly observed indication for QT interval monitoring with 62% percent of patients having been given at least one proarrhythmic drug; 25% of patients were administered 2 or more

proarrhythmic drugs. Twenty-seven (2%) were administered 5 proarrhythmic drugs (Table 15).

Table 15. Number of Proarrhythmic Drug Administrations, by Sex and Overall.

Number of QT drugs	Men		Women		Overall	
	n	%	n	%	n	%
0	346	40.9	241	34.9	587	38.2
1	283	33.4	269	39.0	552	35.9
2	144	17	115	16.7	259	16.9
3	40	4.7	39	5.7	79	5.1
4	21	2.5	12	1.7	33	2.1
5	11	1.3	13	1.9	24	1.6
6	2	0.2	1	0.1	3	0.2

When the number of AHA indications per patient was calculated, 41.2% had 1 indication for QT interval monitoring, 25.6% had 2 indications, and 6.4% had 3 - 4 indications. Twenty seven percent of patients did not have any indications for QT interval monitoring. Overall, 73.3% of the patients admitted to a cardiac monitoring unit during the two month investigation had at least 1 indication for QT interval monitoring.

sex based analysis. Women received significantly more proarrhythmic drugs than men (65.1% v 59.1%, *Fisher's exact p* = .018), had significantly more episodes of low serum potassium (39.7% v 30.5%, *Fisher's exact p* < .0005), and more episodes of low serum magnesium (14.5% v 9.1%, *Fisher's exact p* = .001). Consequently, the proportion of women with AHA indications for QT interval monitoring (74%) was significantly greater than that of men (64.8%). The Fisher's exact test p value was .001.

Research Question 3. Are the AHA indications for QT interval monitoring effective in identifying patients that at are at risk for developing QT interval prolongation while admitted to a unit providing continuous cardiac monitoring?

Of the 1039 patients remaining after exclusions (see methods), 69% had at least one indication for QT interval monitoring. A conservative method was used to establish those with QT interval prolongation (Figure 12). A total of 24.3% (252) of patients had at least one episode of verified QT interval prolongation beyond 500 msecs lasting 15 minutes or longer. Overall, 1.5% (n = 16) of patients had a sustained QTc interval longer than 500 msecs (*M* = 431.70 msecs, *SD* 28.10, *Median* 431.00 msecs). A significant relationship existed between AHA indications and QT interval prolongation. The 2-sided Fisher's exact test p value was < .0005. A greater proportion of patients with AHA indications for QT interval monitoring had an episode of QT interval prolongation than patients without AHA indications (31.2% v 8.7%). To assess whether having more than 1 AHA indication increases a patient's odds of developing QT interval prolongation a binary logistic regression was performed.

Patients were entered into 1 of 4 groups depending on their number of AHA indications: No AHA indications, 1 AHA indication, 2 AHA indications, or 3 or more AHA indications. A significant relationship was found ($x^2 = 99.12$, *df* 3, $p < .0005$). Patients with 1 AHA indication for QT interval monitoring had 3 times the odds for QT interval prolongation than those without AHA indications (*OR* = 3.23, *95% C.I.* 2.6 – 5.05). Patients with 2 AHA indications had 7 times the odds for QT interval prolongation than those without AHA indications (*OR* = 7.33, *95% C.I.* 4.6 – 11.68), and patients with

3 or more AHA indications had 9 times the odds for QT interval prolongation than those without any AHA indications (*OR* = 9.19, *95% C.I.* 4.8 – 17.40).

sex based analysis. Seventy-four percent of women had indications for QT interval monitoring, 29.1% experienced an episode of QT interval prolongation. Women with AHA indications for QT interval monitoring had significantly more QT interval prolongation than women without AHA indications (34.4% v 13.8%, *Fisher's exact p* < .0005). This relationship was also seen in men. Sixty-four percent of men had AHA indications for QT interval monitoring and 20.1% had QT interval prolongation. Men with AHA indications for QT interval monitoring had significantly more QT interval prolongation than those without AHA indications (28.2% v 5.5%, *Fisher's exact p* < .0005).

accuracy of aha practice standards: As a tool to identify patients that are at risk for developing QT interval prolongation, the sensitivity and specificity of the AHA indications for QT interval monitoring were 88.9% and 37.1% respectively within this sample. The positive predictive value of this was 31.2% and the negative predictive value was 91.3%.

Research Question 4. What are the demographic and clinical variables that contribute to a model that best predicts those patients admitted to a unit providing continuous cardiac monitoring who experience QT interval prolongation?

Logistic regression was used to identify the demographic and clinical variables that best predicted patients developing QT interval prolongation. The dependent variable was QT interval prolongation beyond 500 msecs for 15 minutes or longer; this was a

dichotomous outcome variable. Univariate analyses were completed comparing demographic and clinical variables with the dependent outcome variable (Table 16).

Univariate analysis revealed that those with QT interval prolongation were more likely to be women, with a lower body surface area, longer QT interval on initial 12 lead electrocardiogram, more likely to have a history of stroke, history of hypertension, history of diabetes, history of renal disease, history of liver disease, as well as more episodes of low serum sodium, low serum chloride, low serum calcium, low serum potassium, and higher serum glucose, higher serum creatinine, higher serum blood urea nitrogen. Also a greater proportion had been administered at least one proarrhythmic drug.

Number of proarrhythmic drugs administered ($x^2 = 87.716$, df 4, $p < .0005$) was predictive of QT interval prolongation. Patients administered 4 or more proarrhythmic drugs, had 16 times greater odds of developing QT interval prolongation than those not administered any proarrhythmic drugs (*OR* = 16.39, *95% C.I.* 7.28 – 36.90). The next best univariate predictor for QT interval prolongation was a serum potassium level below 3.5 mmol/L. Patients with a low serum potassium level were 3 times more likely to develop QT interval prolongation than those with normal potassium levels (*OR* = 3.30, *95% C.I.* 2.45 – 4.44, *Wald* = 61.45, $p < .0005$). All variables significant at the $p = .2$ level were included in a multivariate logistic regression.

Table 16. Univariate Analyses with QT Interval Prolongation

Variable	QT Normal	QT Prolonged	*p*
Age (in years)	59.88	61.55	.190
Body Surface Area (m^2)	1.92	1.86	.008
Initial systolic BP (mmHg)	127.83	127.82	.997
Initial diastolic BP (mmHg)	69.41	69.18	.848
QTc on initial electrocardiogram (msecs)	424.34	443.23	< .0005
Mean heart rate (beats per minute)	80.01	81.65	.116
	%	**%**	
History of heart failure	10.3	11.9	.483
History of myocardial infarction	8.5	9.9	.525
History of coronary artery disease	18.9	18.7	1.000
History of cerebrovascular accident	12.0	19.0	.006
Historyof hypertension	51.2	58.7	.043
History pulmonary disease	15.7	17.9	.433
History hyperlipidemia	33.5	33.3	1.000
History diabetes (all types)	19.1	29.0	.001
History renal disease (all types)	9.7	15.9	.008
History liver disease (all types)	4.8	9.5	.009
History depression	11.3	9.9	.644
History hypothyroid disease	9.4	13.5	.075
Low serum sodium	39.1	53	< .0005
Low serum chloride	11.4	20.9	< .0005
Low serum calcium	85.9	95.2	< .0005
Low serum potassium	25	52.6	< .0005
Low serum magnesium	14	18.3	.151
High serum glucose >200 mg/dL	13.2	31.7	< .0005
High serum creatinine	18.1	33.7	< .0005
High serum blood urea nitrogen	24.2	37.3	< .0005
High serum thyroid stimulating hormone	9	13.9	.267

E.F. %	n	x^2	*df*	*p*	Wald	P	Exp(B)	Low	High
	422	2.796	2	.247					
Normal					2.860	.239			
Mild					2.812	.094	1.867	0.900	3.874
Severe					0.002	.960	0.982	0.490	1.969

# proarrh. drugs	n	x^2	*df*	*p*	Wald	P	Exp(B)	Low	High
	1039	89.15	5	.000					
0					77.76	.000			
1					19.13	.000	2.198	1.544	3.13
2					15.21	.000	2.431	1.556	3.80
3					40.52	.000	8.602	4.434	16.69
4					21.36	.000	11.355	4.053	31.81
5					25.23	.000	26.839	7.434	96.89

A significant model was found ($n = 761$, $x^2 = 139.706$, df 15, $p < .0005$) containing 9 variables (Table 17). The overall model accounted for 16% - 24% of the total variance of QT interval prolongation (*Cox & Snell R Square* .168 & *Nagelkerke R Square* .248). The strongest predictor for QT interval prolongation was the number of proarrhythmic drugs administered (*Wald* = 21.491, *df* 4, $p < .0005$). Patients receiving 1 proarrhythmic drug had 1.5 times the odds for QT interval prolongation than those not receiving any proarrhythmic drugs (*OR* = 1.59, $p = .043$). Patients who received 3 proarrhythmic drugs had almost 4.5 times the odds for QT interval prolongation than those not receiving any (*OR* = 4.43, *95% C.I.* 1.93 – 10.20). Patients with 4 proarrhythmic drugs had nearly 6 times the odds for QT interval prolongation, versus those not receiving any (*OR* = 5.93, *95% C.I.* 2.24 – 15.71), independent of all other variables.

Table 17. Binary Logistic Regression: QT Interval Prolongation Predictors.

Variables	**Wald**	**df**	***p***	**Exp(B)**	**95% C.I.**	
Age (< 39 yrs)	5.948	3	.114			
Age (40 – 49 yrs)	2.490	1	.115	1.869	.859	4.064
Age (50 – 64 yrs)	5.827	1	.016	2.240	1.164	4.310
Age (> 65 yrs)	4.393	1	.036	1.991	1.046	3.790
Sex	8.111	1	.004	1.726	1.186	2.513
Hx of cerebrovascular accident	8.005	1	.005	2.085	1.253	3.469
Hx of hypothyroid	4.327	1	.038	1.838	1.036	3.263
Low serum calcium	5.984	1	.014	3.076	1.250	7.566
Low serum potassium	15.294	1	.000	2.155	1.467	3.167
High serum creatinine	8.655	1	.003	1.881	1.235	2.864
Serum glucose (<124 mg/dL)	7.961	2	.019			
Serum glucose (125-199 mg/dL)	2.913	1	.088	1.514	.940	2.439
Serum glucose (>200 mg/dL)	7.958	1	.005	2.259	1.282	3.980
0 Proarrhythmic drugs	21.491	4	.000			
1 Proarrhythmic drug	4.113	1	.043	1.588	1.016	2.482
2 Proarrhythmic drugs	2.111	1	.146	1.503	.867	2.606
3 Proarrhythmic drugs	12.253	1	.000	4.432	1.926	10.200
4 Proarrhythmic drugs	12.848	1	.000	5.933	2.241	15.708

The second strongest predictor for QT interval prolongation was a serum potassium level below 3.5 mmol/L (*Wald* = 15.294, *df* 1, $p < .0005$). Patients with an episode of low serum potassium had twice the odds for QT interval prolongation than those with normal or high serum potassium (*OR* = 2.15, *95% C.I.* 1.47 – 3.17). It was decided a priori to control for age and thus, age remained in the model despite not being significant (*Wald* = 5.948, *df* 3, $p = .114$). In total, the variables significantly predicting QT interval prolongation beyond 500 msecs for 15 minutes or more during admittance to a hospital unit providing continuous cardiac monitoring were: female sex, number of proarrhythmic drugs administered, low serum potassium, high serum glucose, high serum creatinine, low serum calcium, history of prior stroke, and history of hypothyroid disease.

Due to a small number of patients admitted to hospital after a drug overdose or with a history of Long QT Syndrome, these variables were excluded from statistical analyses. Additionally, as not all patients had an initial 12 lead electrocardiogram, serum magnesium level, serum TSH level, or ejection fraction measurement, these variables were analyzed separately. Their inclusion into the larger statistical model would limit the sample size of the analysis.

qtc interval group on initial 12 lead electrocardiogram. A total of 538 patients had data on all variables when QT interval on initial 12 lead electrocardiogram was analyzed. As the total number of patients decreased, not all previous independent predictors were significant. In this model female sex, low serum calcium, low serum potassium, high serum creatinine, and number of proarrhythmic drugs administered, remained independent predictors for QT interval prolongation. QTc interval on initial 12 lead electrocardiogram was categorized into 4 groups and added to the model. This model was

significant, with 7 predicting variables (x^2 = 129.585, *df* 14, $p < .0005$). As expected, QTc interval group on initial 12 lead electrocardiogram was predictive of future QT interval prolongation (*Wald* = 33.724, *df* 3, $p < .0005$). The odds for QT interval prolongation increased progressively by group. Compared to those with an initial 12 lead QT interval below 440 msecs, patients with a QT interval on initial 12 lead electrocardiogram between 441 msecs – 460 msecs had 3 times the odds for QT interval prolongation (*OR* = 2.94, *95% C.I.* 1.63 – 5.29). Patients with initial QT interval between 461 msecs – 480 msecs had 3.5 times the odds for QT interval prolongation (*OR* = 3.68, *95% C.I.* 1.94 – 7.00), while those with an initial QTc interval greater than 480 msecs on initial 12 lead electrocardiogram had nearly 7 times the odds for QT interval prolongation (*OR* = 6.94, *95% C.I.* 2.83 – 17.01), with adjustment for all other variables. Overall, the QT interval on the initial 12 lead ECG was a significant predictor for QT interval prolongation.

ejection fraction. When ejection fraction was analyzed, 326 patients had complete data. As the total number of patients decreased, previously significant predictors were no longer significant. In the overall model with the reduced number of patients, female sex, history of stroke, low serum calcium, low serum potassium, high serum creatinine, and number of proarrhythmic drugs administered, remained significant predictors for QT interval prolongation. When ejection fraction was added to this model it was not significant (*Wald* = 1.331, *df* 2, $p = .514$). Ejection fraction was not a significant predictor of QT interval prolongation in a fully adjusted model.

magnesium. When magnesium was analyzed, 581 patients had complete data. As the total number of patients decreased, previously significant predictors were no longer significant. In the overall model with the reduced number of patients (n = 581), female

sex, history of stroke, low serum calcium, low serum potassium, high serum glucose, high serum creatinine, and number of proarrhythmic drugs administered, remained significant predictors for QT interval prolongation. Within this fully adjusted model, serum magnesium below 1.49 mEq/L was not a significant independent predictor for QT interval prolongation (*Wald* < 0.0005, $p = .99$).

thyroid stimulating hormone. When TSH was analyzed, 173 patients had complete data. As the total number of patients decreased, previously significant predictors were no longer significant. In the overall model with the reduced number of patients (n = 173), female sex, history of stroke, low serum potassium, and high serum glucose remained significant predictors for QT interval prolongation. When TSH is added to the fully adjusted model it was not a significant predictor of QT interval prolongation (*Wald* = 1.784, $p = .182$).

sex based analysis. Four hundred and seventeen male patients had complete data for all variables previously shown to be significant independent predictors of QT interval prolongation. The overall model involving only men was significant ($x^2 = 70.598$, *df* 10, $p < .0005$). Variables predicting QT interval prolongation in males was similar to the larger overall model: low serum potassium, high serum glucose, and number of proarrhythmic drugs administered. In women (n = 344, $x^2 = 52.173$, *df* 8, $p < .0005$), history of prior stroke, low serum potassium, high serum glucose, and blood urea nitrogen were significant predictors of QT interval prolongation.

Research Question 5. Is QT interval prolongation associated with a) all-cause in-hospital mortality, b) increased length of hospitalization and cardiac monitoring time, c) critical intervention (code blue, medical rapid response), and d) device intervention (pacemaker, interval cardiac defibrillator).

Mortality. In all, 371 patients were needed for the analysis to have 80% power: 352 alive at discharge and 18 with all-cause mortality. In this investigation 42 patients died from all-causes. A 2 x 2 contingency table was used to determine if QT interval prolongation was associated with all-cause in-hospital mortality. A significant relationship existed (*Fisher's exact* $p < .0005$). A greater proportion of patients with an episode of QT interval prolongation died than those without QT interval prolongation (8.7% v 2.6%).

To assess if QT interval prolongation was an independent predictor of all-cause in-hospital mortality, demographic and clinical variables were used in univariate analysis with all-cause in-hospital mortality, a dichotomous dependent outcome variable (Table 18). Patients with all-cause mortality were more likely to be older, had a lower initial systolic and diastolic blood pressure, a higher heart rate, a greater proportion with glucose over 200 mg/dL, a greater proportion of high serum creatinine, high serum blood urea nitrogen, greater proportion with QT interval prolongation, and a greater proportion receiving proarrhythmic drugs. An equal proportion of men and women died.

Variables significant on univariate analyses (at $p < .20$) were entered into a model. Non-contributory variables were removed separately from least significant to most, one at a time, until only significant variables remained.

Table 18. Univariate Analyses with All-Cause In-Hospital Mortality

Variable	Alive	Dead	*p*
Age (in years)	59.87	68.52	.003
Body Surface Area (m^2)	1.911	1.985	.196
Initial systolic BP (mmHg)	128.2	119.19	.009
Initial diastolic BP (mmHg)	69.60	64.24	.021
QTc on initial electrocardiogram (msecs)	429.34	437.43	.153
Mean heart rate (beats per minute)	79.64	92.26	<.0005
Mean QTc interval (msec)	430.93	442.245	.065
	%	**%**	
Episode of bradycardia (< 40 bpm)	3.8	9.8	.078
QT interval prolongation	22.4	50	<.0005
History of heart failure	10.5	11.9	.796
History of myocardial infarction	8.7	14.3	.259
History of coronary artery disease	18.9	19	1.000
History of cerebrovascular accident	13.3	23.8	.640
Historyof hypertension	53.3	52.4	1.000
History pulmonary disease	15.9	16.7	.831
History hyperlipidemia	33.7	38.1	.618
History diabetes (all types)	21.3	31.0	.178
History renal disease (all types)	10.7	11.9	.798
History liver disease (all types)	5.9	4.8	1.000
History depression	10.8	11.9	.799
History hypothyroid disease	10.3	9.5	1.000
Low serum sodium	41.5	50	.338
Low serum chloride	13	21.4	.159
Low serum calcium	87.7	97.6	.510
Low serum potassium	30.7	47.6	.270
Low serum magnesium	15.3	10.0	.496
High serum glucose >200 mg/dL	16.7	40.5	<.0005
High serum creatinine	19.6	61.9	<.0005
High serum blood urea nitrogen	23.9	83.3	<.0005
High serum thyroid stimulating hormone	9.2	30.0	.069

# proarrh. drugs	n	x^2	*df*	*p*	Wald	P	Exp(B)	Low	High
	1012	26.82	4	.000					
0					77.76	.000			
1					2.299	.129	2.074	.808	5.323
2					12.216	.000	5.463	2.108	14.155
3					2.299	.000	11.091	3.524	34.904
4					12.311	.000	10.167	2.783	37.135
5					25.23	.000	26.839	7.434	96.89

The overall model was significant with 6 predictors (Table 19) (n = 726, x^2 = 85.448, *df* 13, $p < .0005$), and described between 11% and 40% of the total variance seen

in all-cause mortality (*Cox & Snell R square* & *Nagelkerke R square* values). The strongest predictor for all-cause in-hospital mortality was blood urea nitrogen (*Wald* = 22.723, *df* 1, $p < .0005$). Those with serum blood urea nitrogen above 25 mg/dL had 17 times the odds for death of those with blood urea nitrogen below 25 mg/dL (*95% C.I.* 5.37 – 56.17). Number of proarrhythmic drugs administered was the second strongest predictor of all-cause mortality (*Wald* = 11.43, *df* 4, $p = .022$). Patients administered 1 proarrhythmic drug had nearly 2.5 times the odds for all-cause mortality than those not administered any proarrhythmic drug (*OR* = 2.40, *95% C.I.* 2.05 – 39.51), while those administered 4 or more proarrhythmic drugs had 9.5 times the odds for all-cause mortality than those not administered any proarrhythmic drugs (*OR* 9.66, *95% C.I.* 1.45 – 64.23), accounting for all other variables. Importantly, QT interval prolongation was a significant independent predictor of all-cause mortality. Patients with QT interval prolongation had nearly 3 times the odds for all-cause mortality than patients without QT interval prolongation (*OR* = 2.99, *Wald* = 4.640, *df* 1, $p = .031$, *95% C.I.* 1.10 – 8.10).

Table 19. Binary Logistic Regression: Predictors of All-Cause In-Hospital Mortality

Variables	**Wald**	**df**	***p***	**Exp(B)**	**95% C.I.**	
Age (< 39 yrs)	5.479	3	.140			
Age (40 – 49 yrs)	0.066	1	.797	.755	.088	6.477
Age (50 – 64 yrs)	0.460	1	.498	.522	.080	3.417
Age (> 65 yrs)	0.705	1	.401	2.123	.366	12.308
Sex	0.111	1	.739	.739	.406	3.563
Hx of cerebrovascular accident	6.647	1	.010	4.674	1.447	15.093
Body surface area	3.865	1	.049	6.032	1.006	36.186
High serum BUN	22.723	1	.000	17.369	5.371	56.174
QT interval prolongation	4.640	1	.031	2.989	1.104	8.096
Mean heart rate	7.111	1	.008	1.048	1.012	1.085
0 Proarrhythmic drugs	11.434	4	.022			
1 Proarrhythmic drug	1.375	1	.241	2.394	.556	10.298
2 Proarrhythmic drugs	8.486	1	.004	9.006	2.053	39.512
3 Proarrhythmic drugs	4.279	1	.039	6.856	1.106	42.489
4 Proarrhythmic drugs	5.507	1	.019	9.661	1.453	64.234

Overall independent predictors for all-cause in-hospital mortality were high blood urea nitrogen, number of proarrhythmic drugs administered, higher mean heart rate, larger body surface area, history of prior stroke, and an episode of QT interval prolongation greater than 500 msecs for 15 minutes or longer.

Length of QT interval monitoring. The number of QT interval values produced for each patient during their length of stay can be used as a proxy to estimate the total length of cardiac monitoring time. Patients with an episode of QT interval prolongation (n = 252) had significantly longer mean monitoring time (M = 123.61 hours) than patients who did not have QT interval prolongation (n = 787, M = 46.42 hours) (t = 8.689, df 301.953, $p < .0005$). Patients with QT interval prolongation had on average more than 77.18 hours more cardiac monitoring than those without QT interval prolongation (*95% C.I.* 59.71 hrs – 94.68 hrs).

Length of hospital admission. Patients with an episode of QT interval prolongation had significantly longer hospital stays (M = 11.53 days) than patients who did not have QT interval prolongation (M = 5.52 days) (t = 5.896, df 303.634, $p < .0005$). Patients with QT interval prolongation had on average 6 days longer hospital admission than those without QT interval prolongation (*95% C.I.* 4 days – 8 days). Univariate analysis was performed for all demographic and clinical variables with length of hospital stay, a continuous variable (n = 975) (Table 20). Significant variables at the $p < .20$ level were entered into a multiple regression. A significant overall model was determined (F = 29.106, df 9,993, $p < .0005$), with an R^2 of .209. Subjects predicted length of hospital stay was equal to -5.164(constant) – 1.761(female sex) – 0.022(age) – 2.269(prior myocardial infarction) + 4.292(low serum potassium) + 3.346(low serum sodium) + 1.712(high

serum BUN) + 3.369(episode of QT interval prolongation) + 3.235(administered a proarrhythmic drug) + 0.108(per unit of mean heart rate). Importantly, in a fully adjusted model, QT interval prolongation beyond 500 msecs lasting 15 minutes or longer increased a patient's length of stay 3.37 days. QT interval prolongation was a significant independent predictor of length of hospital stay.

Table 20. Univariate Analysis with Length of Hospitalization

Variable	**Stat** R^2	***p***
Age (in years)	-.082	.008
Body Surface Area (m^2)	.026	.468
Weight	.36	.278
Initial systolic BP (mmHg)	-.52	.094
Initial diastolic BP (mmHg)	.039	.207
QTc on initial electrocardiogram (msecs)	-.091	.014
Mean heart rate (beats per minute)	.251	<.0005
Mean QTc interval (msec)	-.011	.720
	t	
Sex	.459	.646
Episode of bradycardia (< 40 bom)	-1.695	.098
QT interval prolongation	-5.896	<.0005
History of heart failure	-.683	.495
History of myocardial infarction	6.574	<.0005
History of coronary artery disease	2.995	.003
History of cerebrovascular accident	-1.561	.119
Historyof hypertension	1.755	.080
History pulmonary disease	-.814	.416
History hyperlipidemia	1.923	.055
History diabetes (all types)	-1.406	.160
History renal disease (all types)	-1.282	.202
History liver disease (all types)	-1.692	.095
History depression	.444	.766
History hypothyroid disease	1.006	.315
Low serum sodium	-7.386	< .0005
Low serum chloride	-4.085	< .0005
Low serum calcium	-5.289	< .0005
Low serum potassium	-7.469	<.0005
Low serum magnesium	-2.658	.008
High serum glucose >200 mg/dL		
High serum creatinine	-2.767	.006
High serum blood urea nitrogen	-2.967	.003
High serum thyroid stimulating hormone	-.079	.937
	F	
Glucose (3 levels)	29.016	<.0005
Race (5 levels)	1.167	.324
Ejection Fraction (3 levels)	.158	.854

Critical interventions. There were 16 (1.5%) *code blue team* requests and 21 (2 %) *rapid response team* requests, for 31 (3%) medical emergencies and 6 (< 1%) cardiopulmonary resuscitations. These requests were grouped into a single *critical intervention* variable (n = 37). To assess whether a relationship existed between QT interval prolongation and need for critical intervention, a 2 x 2 contingency table was used. A significant relationship existed, those with QT interval prolongation had significantly greater proportions of critical intervention (7.1%) than those with normal or short QT interval (2.4%, *Fisher's exact p* = .001).

Univariate analysis was used to determine differences between patients requiring critical intervention and those that do not (Table 21). Patients requiring critical intervention had a lower initial systolic blood pressure, higher mean heart rate, greater proportion of pulmonary disease, greater proportion of low serum sodium, greater proportion of low serum potassium, greater proportion of high glucose, greater proportion of high BUN, greater proportion receiving proarrhythmic drugs, and a greater proportion with QT interval prolongation above 500 msecs for 15 minutes or longer. The need for critical intervention was not related to sex, or age.

Variables significant on univariate analyses (at $p < .20$) were entered into a model. Non-contributory variables were removed separately from least significant to most, one at a time, until only significant variables remained.

Table 21. Univariate Analysis with Critical Intervention

Variable	None	Critical Intervention	*p*
Age (in years)	60.15	63.79	0.238
Body Surface Area (m^2)	1.915	1.867	0.427
Initial systolic BP (mmHg)	128.18	118.58	0.009
Initial diastolic BP (mmHg)	69.44	67.24	0.369
QTc on initial electrocardiogram (msecs)	429.27	430.86	0.777
Mean heart rate (beats per minute)	80.17	86.56	0.007
Mean QTc interval (msec)	431.34	432.78	0.762
	%	**%**	
Episode of bradycardia (< 40 bom)	4.0	8.1	0.192
QT interval prolongation	23.1	47.4	0.001
History of heart failure	10.9	5.3	0.420
History of myocardial infarction	8.8	10.5	0.768
History of coronary artery disease	19.3	7.9	0.091
History of cerebrovascular accident	13.6	15.8	0.635
Historyof hypertension	53.5	39.5	0.099
History pulmonary disease	15.7	28.9	0.041
History hyperlipidemia	34	18.4	0.053
History diabetes (all types)	21.3	26.3	0.426
History renal disease (all types)	11.2	10.5	1.000
History liver disease (all types)	5.8	7.9	0.487
History depression	11.1	7.9	0.791
History hypothyroid disease	10.4	10.5	1.000
Low serum sodium	41.8	60.5	0.029
Low serum chloride	13.3	23.7	0.088
Low serum calcium	87.8	97.4	0.076
Low serum potassium	30.8	57.9	0.001
Low serum magnesium	15	18.9	0.485
High serum glucose >200 mg/dL	16.9	39.5	0.001
High serum creatinine	21.7	26.3	0.548
High serum blood urea nitrogen	26.7	47.4	0.008
High serum thyroid stimulating hormone	10	21.4	0.180

The final overall model was significant with 6 predictors (Table 22) (x^2 = 50.97, *df* 12, $p < .0005$), and described between 5% and 18% of the total variance in need for critical intervention (*Cox & Snell R square* & *Nagelkerke R square* values). The strongest predictor for critical intervention was the number of proarrhythmic drugs administered (*Wald* = 16.67, *df* 4, p =.002). Those administered 3 proarrhythmic drugs, and those administered 4 or more, had 12 times and nearly 9 times the odds respectively, of requiring critical intervention, versus those not receiving any proarrhythmic drugs, accounting for all other variables (*95% C.I.* 3.25 – 46.02 & 2.10 – 38.16, respectively).

Serum glucose group was the second highest predictor for critical intervention (*Wald* = 8.36, *df* 2, *p* = .015). There was no difference in the odds for critical intervention between patients whose highest serum glucose level was between 125 mg/dL and 199 mg/dL, and those patients below 125 mg/dL (*OR* = 2.89, *95% C.I.* 0.82 – 10.20), but patients with a serum glucose above 200 mg/dL had 6 times the odds for critical intervention, than patients whose highest serum glucose was lower than 125 mg/dL (*OR* = 6.05, *95% C.I.* 1.64 – 22.32). Despite not being significant contributors, sex and age remained in the overall model as it was decided a priori to adjust for both.

Table 22. Binary Logistic Regression: Predictors of Critical Intervention

Variables	**Wald**	**df**	***p***	**Exp(B)**	**95% C.I.**	
Age (< 39 yrs)	3.657	3	.301			
Age (40 – 49 yrs)	.392	1	.531	1.628	.354	7.480
Age (50 – 64 yrs)	1.259	1	.262	2.181	.558	8.519
Age (> 65 yrs)	2.945	1	.086	3.124	.850	11.474
Sex	.131	1	.718	1.139	.563	2.305
Initial Systolic BP	4.815	1	.028	.982	.966	.998
Hyperlipidemia	4.801	1	.028	.352	.139	.896
Glucose (< 124 mg/dL)	8.363	2	.015			
Glucose (125 – 199 mg/dL)	2.703	1	.088	1.514	.940	2.439
Glucose (> 200 mg/dL)	7.314	1	.005	2.259	1.282	3.980
0 Proarrhythmic drugs	16.672	4	.022			
1 Proarrhythmic drug	3.502	1	.061	3.000	.949	9.479
2 Proarrhythmic drugs	4.343	1	.037	3.854	1.084	13.705
3 Proarrhythmic drugs	13.738	1	.000	12.240	3.255	46.023
4 Proarrhythmic drugs	8.755	1	.003	8.942	2.095	38.162

Overall, the variables predicting patients requiring critical intervention during this investigation were number of proarrhythmic drugs administered, serum glucose above 200 mg/dL, low systolic blood pressure on admission, and history of hyperlipidemia. Importantly, QT interval prolongation beyond 500 msecs for 15 minutes or longer was not a significant predictor for critical intervention.

Device intervention. Of the 1039 patients monitored during the investigation period, 36 underwent procedures in the electrophysiology (EP) laboratory: 6 pacemaker insertions, 6 implantable cardiac devices, 1 ventricular tachycardia related ablation, 16 non-ventricular tachycardia related ablations, and 7 *other* procedures (for example EP study). A 2 x 2 contingency table was used to determine if QT interval prolongation was associated with the needing an EP laboratory procedure. No significant relationship was found. There was no difference in the proportion of EP laboratory procedures between those with QT interval prolongation (2.4%) and those without (3.8%, *Fisher's exact value p* =.328).

CHAPTER 5

DISCUSSION

Investigation of Nurses

Does a QT interval intensive education class improve nurses' QT interval related knowledge?

Though evident for many years with quinidine, it was not until publication of the CAST study in 1992 that the potentially proarrhythmic effects of certain drugs became clear. In 2004 the AHA recommended for the first time that clinicians perform QT interval monitoring for patients at risk of TdP. These recommendations are especially relevant to nurses as they are the primary clinicians administering proarrhythmic drugs and providing continuous cardiac monitoring. However, there is little research evaluating the ability of nurses to perform QT interval monitoring.

As this is a new recommendation, we set out to evaluate whether nurses working on units providing continuous cardiac monitoring, possess the knowledge and skills necessary to implement the AHA practice standards as they relate to QT interval monitoring. The only other investigation to date evaluating nurses' QT interval monitoring ability was conducted as this study's pilot study. Here 73% of participating graduate nurses (n = 31) indicated that they monitor the QT interval regularly, but no one was able to perform a manual QTc interval calculation (Pickham & Drew, 2007).

This investigation was conducted at a renowned west coast academic medical center recently designated as a Magnet Facility for outstanding nursing services. Our

sample (n = 391) was well educated with over 75% of participating nurses possessing a Bachelors level of nursing education or greater, and experienced, with over 70% having at least 5 years of nursing experience.

Previous studies have evaluated clinicians QT interval monitoring abilities. Marshall and Myles (2005) asked anesthetists to identify the consequence of QT interval prolongation; sixty-five percent of trainee physicians and 70% of consultant physicians correctly identified TdP. In another study, La Pointe et al. (2003) presented a combination of drugs to participants and asked them to identify the most likely to prolong the QT interval; fifty one percent of participants responded correctly. In our investigation, 60% of nurses knew that QT interval prolongation was associated with TdP, and 88 % knew to monitor the QT interval at least once per shift. An important aspect of QT interval monitoring is adjusting for the affect of heart rate. Only 35% of nurses knew that the QTc interval was the QT interval corrected for heart rate.

Other important aspects of QT interval monitoring are: identifying who is at-risk for TdP, signs of impending TdP, and confounders to accurate QT interval measurement. We found on pretest that 59% of nurses correctly identified a patient requiring QT interval monitoring and 35% correctly identified a group of diseases that were associated with QT interval prolongation, 28% were able to identify the electrocardiographic sign least associated with TdP, and 55% identified a Bundle Branch block as being a confounder to QT interval duration.

Previous studies evaluating physicians' abilities to measure the QT interval reveal success rates between 10% - 89%, depending on the participant's specialty (Al-

Khatib et al., 2005; LaPointe et al., 2003; Marshall & Myles, 2005; Viskin et al., 2005). When asked to calculate the QTc interval, these studies found success rates between 5% (Solomons et al., 2008) and 80% (Viskin et al., 2005). This latter study found that 50% of cardiologists and 40% of non-cardiologist physicians correctly calculated the QTc interval; much fewer, less than 25% correctly classified the QT interval on four electrocardiogram examples as being either normal or prolonged.

In our investigation we tried to mimic the clinical situation, asking nurses first to mark the QT and RR intervals on a single channel rhythm strip, then measure both marked intervals, and apply any known QT interval correction formula manually to determine the QTc interval. Similar to physician samples, we found that 65% of nurses correctly marked the QT interval, and 46 % correctly measured it. The vast majority of participating nurses (94%) at baseline were unable to perform a QTc interval calculation.

After the education class a significant improvement was seen in both the marking (91% v 65%) and measuring (84% v 46%) of the QT interval. Most importantly, there was a significant improvement in the proportion of correct responses when asked to provide the QTc interval value. After the education class 52% of nurses correctly calculated the QTc interval, versus 6% at pre test. A novel finding of this investigation is that one-third of nurses measured the QT and RR intervals correctly but during calculation of the Bazett's formula, erred. This is interesting as it demonstrates that a large proportion of the error associated with manual measurement in this study, was not due to incorrect measurement, but due to miscalculation. As such, nurses should use semi-automated or fully automated methods, to avoid performing this calculation manually.

The education intervention improved nurses' knowledge significantly, regardless of years of experience or highest level of education, all nurses after education performed QT interval monitoring equally. At baseline though, mean QT interval score was low and differences existed between units and education groups. Several factors exist that may explain these. First, the majority of our sample had greater than 5 years nursing experience. Therefore, as this investigation was conducted in late 2007 we could assume that the majority of nurses completed their nursing education before 2002, nearly 2 years before the AHA practice standards recommended routine QT interval monitoring. It is a real possibility that QT interval monitoring was not included in the nursing curriculum at that time. Those with a Master's level of education may have recently obtained this level of education and had instruction on QT interval monitoring as part of their advanced studies. Consequently, the majority of nurses within our sample had not received formal QT interval monitoring training.

Second, hospital protocols for QT interval monitoring were not universal and each unit, depending upon clinician aptitude, conducted surveillance for TdP differently. Only patients being administered a small selection of known proarrhythmic drugs, for example dofetilide or sotalol, were monitored for QT interval prolongation. This was performed by repeating a 12 lead electrocardiogram at an interval determined by the physician, for example 20 minutes post drug administration. Once produced, the QT interval was measured without adjustment for heart rate by the nurse, or the electrocardiogram was provided to the physician for review and calculation of the QTc interval; the majority of nurses were not required to calculate the QTc interval.

Third, nurses within the cardiac monitoring unit (CCU) had experience with administering potentially proarrhythmic drugs and therefore had had exposure to QT interval monitoring as described above. This was evident from pre test results, with nurses from CCU performing better than all other units. Understandably, nurses on units without exposure to QT interval monitoring would have less knowledge and abilities related to this skill.

Finally, when QT interval monitoring is being performed, nurses may be dependent upon the automated QTc interval feature generated by standard 12 lead electrocardiograph machines or use a semi-automated method, as is available within the Philips Intellivue Patient Monitoring System. Dependence on technology reduces nurses' abilities to develop competence with manual QT interval monitoring skills. As the ability of nurses to manually monitor the QT interval was tested within this investigation, there is a real potential for bias and may unfairly classify nurses within our investigation as being unable to perform QT interval monitoring.

Summary

This is the first study to assess nurses' knowledge and skills related to QT interval monitoring. Though similar to physician samples, nurses' manual monitoring of the QT interval, even after an education intervention is shown to be associated with significant error. These were determined to occur mostly while performing a correction for heart rate's affect. A non-manual method for QT interval monitoring may be beneficial. Additionally, the majority of nurses at baseline could not identify a patient with AHA indications for QT interval monitoring. To ensure at-risk patients receive QT

interval monitoring, a system that does not rely on the correct identification of at-risk patients is desirable. Continued education and awareness is needed to improve nurses' QT interval monitoring skills and abilities.

Investigation of Patients

What proportion of patients admitted to a study unit have an AHA indication for QT interval monitoring?

The AHA practice standards identify patients who are *top priority* for QT interval monitoring. Our investigation reveals that 73.3% percent of patients admitted to a hospital unit providing cardiac monitoring (n = 1537) had at least one AHA indication for requiring QT interval monitoring; one in four patients had 2 or more indications for QT interval monitoring. The need for QT interval monitoring was extremely high for all participating cardiac monitoring units (Table 23). Eight out of ten patients required QT interval monitoring in the MST and CICU units.

Table 23. Proportion of Patients with AHA Indications Per Study Unit

Unit	%
CICU	82.2
MST	83.6
CCU	67.7
CIICU	62.6
MSTI	72.5

Administration of a proarrhythmic drug was the most common indication for QT interval monitoring. Drugs listed by the Arizona Center for Education and Research on Therapeutics (Woosley, 2004) as having a known risk of causing TdP or were associated with reports of TdP (lists 1 & 2) were for the purpose of this investigation, determined to be proarrhythmic. The top 5 administered proarrhythmic drugs were ondansetron (Zofran) (n = 583 patients receiving at least 1 dose), levofloxacin (Levaquin) (n = 212), amiodarone (n = 172), haloperidol (Haldol) (n = 106), and tacrolimus (Prograf) (n = 54).

In a similar investigation, Freeman et al. (2008) retrospectively evaluated proarrhythmic drugs administered in intensive care units. In 212,016 patients they found that 2.9% of patients were administered a proarrhythmic drug and 18.6% of these patients had co-administration of a 2nd proarrhythmic drug. The most commonly administered drugs were amiodarone (23.5%), haloperidol (19.8%), and levofloxacin (19.7%). The differences in prevalence between our investigation and Freeman's study can be attributed to the different definitions for a proarrhythmic drug event. They defined a proarrhythmic drug as one that was routinely administered for greater than 24 hours. Within our investigation, any administration of a proarrhythmic drug was deemed to be an event. As such ondansetron (Zofran), an antiemetic administered pro re nata (PRN), was the most commonly administered proarrhythmic drug.

Serum potassium level below 3.5 mmol/L was the second highest indication for QT interval monitoring. Within this sample 34.6% of admitted patients had at least one episode of serum potassium below 3.5 mmol/L. This finding is significantly higher than previously reported. Both the patient sample and the methodology may explain these differences. Results from the National Health and Nutrition Examination Survey showed

that 4.3% of women and 1.7% of men in the US had hypokalemia (Wysowski, Kornegay, Nourjah, & Trontell, 2003). In a study of 2402 preoperative patients, 2.9% had a serum potassium level below 3.5 mmol/L (Wahr et al., 1999), while Trojak et al. (2009) (n = 282) and Lam et al. (2009) (n = 347) studying acute psychiatric patients, found prevalence rates for hypokalemia vary as high as 11% and 20.5% respectively. In contrast to prior studies that collected serum potassium levels at one time point, our investigation used the lowest serum potassium level obtained from any serum laboratory value from the patient's length of stay. Therefore, as we have screened patient's serum potassium levels at multiple time points, it is expected that more cases of hypokalemia are identified. Additionally, our study sample consisted of acute and critically ill patients, and could experience greater proportions of electrolyte disturbances than general medical patients.

The final indication for QT interval prolongation was bradycardia. In our investigation this was defined as a heart rate below 40 beats per minute; determined automatically from the Philips Intellivue Patient Monitoring System. Only 5% of patients experienced an episode of bradycardia. This was equal for men and women.

In addition to establishing the prevalence of AHA indications, this investigation also finds that women are at an even greater risk for TdP than men, during hospitalization. It is known that women account for up to 70% of TdP events (Gussak & Antzelevitch, 2003, p. 318). This is attributed to longer mean QT intervals than those in men (Bazett, 1920; Rautaharju et al., 1992). This investigation finds that women have significantly more AHA indications for QT interval monitoring than men ($p = 0.001$, 77.2% v 70%), due to a significantly greater proportion receiving proarrhythmic drugs

(65.1% v 59.1%, $p = 0.018$) and electrolyte disturbances: low serum potassium (39.7% v 30.5%, $p < 0.0005$) and low serum magnesium (14.5% v 9.1%, $p = 0.001$). Previous studies support this finding (Benoit et al., 2005; Fukui et al., 2002; Wysowski et al., 2003). Consequently, the women's risk for TdP is significantly greater than that of men, especially during hospitalization.

Summary

This investigation demonstrates that the majority of patients (73%) admitted to a unit providing cardiac monitoring had at least one indication, as per the AHA practice standards for QT interval monitoring. Administration of a proarrhythmic drug was the most common indication for QT interval monitoring with 62% of all patients administered at least 1 proarrhythmic drug. Low serum potassium (< 3.5 mmol/L) was the second most likely indication, effecting nearly 35% of all patients. The prevalence of proarrhythmic drug administration and the incidence of hypokalemia were higher than previously reported. In addition we show that over 25% of patients have at least two indications for QT interval monitoring. A discussion on whether this is associated with increased proportions of QT interval prolongation is provided in the next section.

A novel finding in this study is that more women had indications for QT interval monitoring than men. In our sample this was due to a greater proportion of electrolyte disturbances and proarrhythmic drug administration. While reasons for this at this time are unclear, these findings coincide with the known fact that the majority of cases of TdP occur in women.

Are the AHA indications for QT interval monitoring effective in identifying patients that at are at risk for developing QT interval prolongation while admitted to a unit providing continuous cardiac monitoring?

Very little research has been conducted to determine the prevalence of QT interval prolongation in the hospital setting, especially in cardiac monitoring units. Golzari et al. (2007) evaluated 258 patients admitted to a general medical unit, finding 25.2% of patients had a Bazett's corrected QT interval above 450 msecs; 3.5% were above 500 msecs. This was similar to Lubart's et al. (2009) study of 422 geriatric patients. They determined that 27% of admitted patients had a QT interval beyond 470 msecs for women and 450 msecs for men. When we review our initial 12 lead electrocardiograph data, it is similar to that of previous studies. Of the 728 patients with an initial 12 lead electrocardiogram, 2.2% had a QT interval above 500 msecs and 17.3% of patients had a QT interval beyond normal limits (women = 460 msecs, men = 450 msecs).

However from our continuous QT interval monitoring data, the prevalence of QT interval prolongation beyond 500 msecs reached 24%. This is much higher than previously thought and can be evaluated based on a number of factors. First, our investigation was with an acutely ill sample, the risk for QT interval prolongation is much higher than that in larger healthier or general medical populations. Second, the continuous QT interval system uses all available leads to construct a root-mean-squared (RMS) template wave (Helfenbein et al., 2006) - a better representation of global repolarization. As many leads are included in the analysis, automated methods can be longer than those determined manually (Pentti, Rautaharju et al., 2009). Third, our

investigation evaluates QT interval duration at many times points. The majority of studies attempting to determine the prevalence of QT interval prolongation use data obtained from a single 12 lead electrocardiogram. Ten seconds of data is grossly inadequate, considering the multiple acquired factors known to contribute to QT interval duration (Litwin et al., 2008) and natural diurnal variations (Molnar, Zhang, Weiss, Ehlert, & Rosenthal, 1996). The continuous QT interval system evaluates 86,400 seconds of data per day to characterize patients' QT interval duration. Therefore, like serum electrolyte data, with data analyzed over many more time points, it is understandable that more QT interval prolongation is identified. Together these factors contribute to explain the higher prevalence of QT interval prolongation found in our investigation.

As well as identifying the prevalence of QT interval prolongation, this is the first study to evaluate the AHA indications ability to identify those most at risk for QT interval prolongation. Based on our study sample, continuous monitoring system, and manual over read as gold standard, AHA indications for detection of QT interval prolongation had a sensitivity of 88.9%, a specificity of 37.4%, a positive predictive value of 31.2%, and a negative predictive value of 91.3%.

A majority of patients with AHA indications for QT interval monitoring did not develop QT interval prolongation. As there is very little burden placed upon the nurse when providing QT interval monitoring with the continuous QT interval monitoring system, the negative effect of this is minimal. However correlating with a high sensitivity and negative predictive value, our findings show that for every 3 patients indicated QT interval monitoring, 1 will develop QT interval prolongation. Although the AHA indications capture the majority of patients developing QT interval prolongation, these

indications are not ideal. More specific predictors are needed. These are discussed in the following section.

Summary

Our investigation reveals a high prevalence of QT interval prolongation in the acutely ill. The need for QT interval monitoring in this sample is greater than previously expected. This highlights the need for an accurate screening tool to identify those at risk for QT interval prolongation. The AHA indications successfully capture the vast majority of those developing QT interval prolongation, though they lack specificity. The negative effect of this is minimal when using a continuous QT interval monitoring system. However, if relying on manual methods to monitor the QT interval, a lack of specificity results in the monitoring of patients that will not develop QT interval prolongation. More accurate indications are needed.

What are the demographic and clinical variables that contribute to a model that best predicts those patients admitted to a unit providing continuous cardiac monitoring who experience QT interval prolongation?

In determining a model to identify patients developing QT interval prolongation, this investigation both confirms and extends those predictors set out in the AHA practice standards. The best fitting multivariate logistic regression consisted of 9 variables: female sex, number of proarrhythmic drugs administered, low serum potassium, high serum glucose, high serum creatinine, low serum calcium, history of prior stroke, history of hypothyroid disease, and age (kept in despite lacking significance). This investigation confirms already well-known risk factors for QT interval prolongation: female sex,

proarrhythmic drug administration and low serum potassium. Heart rate below 40 beats per minute did not predict QT interval prolongation, and as only 1 patient was admitted for treatment of drug overdose, its predictability for QT interval prolongation could not be evaluated.

In their review of the NHNES III data, Benoit et al. (2005) raises the concern of magnesium being a possible confounder for serum calcium levels. Our data show that there was a positive correlation between serum magnesium and serum calcium levels (r = .408). Physiologically however there is a discrepancy: decreased magnesium levels would increase intracellular calcium. In our adjusted multivariate logistic regression, only low serum calcium was significantly predictive of QT interval prolongation. This was found in other studies (Benoit et al., 2005; Fukui et al., 2003; Sohaib, Papacosta, Morris, Macfarlane, & Whincup, 2009). Therefore, in addition to low serum potassium, serum calcium (non-ionized) below 9 mg/dL should be considered an indication for QT interval monitoring.

In both univariate and multivariate analysis our investigation shows that serum magnesium lower than 1.5 mEq/L is not a significant predictor for QT interval prolongation. This has previously been shown (Sohaib et al., 2008) and is congruent with physiological understanding. Serum magnesium is a poor indicator of intracellular magnesium. The majority of magnesium is sequestered in cells, where among its many functions it regulates potassium extrusion, inhibits calcium influx (Gums, 2004), and is essential in normal ion pump function (Michailova et al., 2004). Hypomagnesemia results in an increase in intracellular sodium, calcium, and loss of intracellular potassium (Vandenberg, 1987). This was demonstrated by Takanaka et al. (1997), finding

hypomagnesemia resulted in prolongation of phase 2 of the action potential. An increase in intracellular calcium can increase the potential for arrhythmias. As such, although not a significant predictor within this investigation, hypomagnesemia should continue to be an indication for QT interval monitoring due to its potential contribution to QT interval prolongation and TdP.

Creatinine is a by-product of muscle breakdown that is filtered in the kidneys and excreted in urine. It is thought to be a better indicator of renal function than blood urea nitrogen, as it is not influenced by diet (Kee, 2009, p. 149). In this investigation, history of renal failure (acute/chronic/end-stage), blood urea nitrogen, and serum creatinine level above 1.5 mg/dL were all significantly associated with QT interval prolongation during univariate analysis. However, within multivariate modeling, only high serum creatinine remained as a significant predictor of QT interval prolongation.

The relationship between creatinine and QT interval prolongation is not well understood. In a meta-analysis of 22 clinical trials involving 3135 patients administered sotalol, creatinine was found to be predictive of TdP (Lehmann, Hardy, Archibald, Quart, & MacNeil, 1996). Clinically, proarrhythmic drugs like sotalol, are often adjusted according to the patient's creatinine clearance. Simplistically, reduced kidney function causes an increase in renal-eliminated proarrhythmic drugs, subsequently increasing the risk for QT interval prolongation. But importantly, patients with renal disease have an elevated risk for cardiovascular related mortality (Salles et al., 2009; Sarnak et al., 2003), most likely due to renal induced ventricular structural changes (Tyralla & Amann, 2002). Within this investigation, the biomarker for renal function, creatinine, significantly predicts the physiological marker for impaired ventricular repolarization, QT interval

prolongation; affirming the existence of a cardio-renal relationship. Further research investigating this relationship is needed.

The relationship between serum glucose and QT interval duration is keenly debated. Studies have linked QT interval prolongation to diabetes (Chugh et al., 2009), high (Fukui et al., 2003) and low serum glucose levels (Suys et al., 2006), as well as fasting glucose (Brown et al., 2001; Grandinetti et al., 2005), and glycosylated hemoglobin (Giunti et al., 2007). The mechanisms behind these relationships are not fully understood (Dekker et al., 2004). Interestingly, Zhang et al. (2003) demonstrated reduced I_{Kr} activity in response to hypo- and hyperglycemia. More recently Hreiche et al. (2009) described diabetes in context to Zhang's results as being a metabolic insult on repolarization reserve. Their research team was successful in extending Zhang's results through potentiating dofetilide's blockade of I_{Kr} with both high and low concentrations of glucose (Hreiche et al., 2009). Evidently, serum glucose levels and QT interval duration are intimately related. A recent clinical study from Australia supports this finding. In analyzing data obtained from 197 critically ill patients, Burkett, Keijzers and Lind (2009) found a significant moderate correlation between serum glucose level and QT interval duration.

Our findings are consistent with these studies. We find that serum glucose is an independent predictor of QT interval prolongation. On multivariate logistic regression, patients with an episode of serum glucose above 200 mg/dL had twice the odds for QT interval prolongation than patients whose highest serum glucose was below 125 mg/dL. Therefore, as an independent predictor of QT interval prolongation, and evidence demonstrating the potentiating affects of glucose on I_{Kr}, the major ion channel blocked by

proarrhythmic drugs, hyperglycemia should be considered an indication for QT interval monitoring. As results from this investigation cannot corroborate the link between low serum glucose and QT interval prolongation, no recommendation regarding hypoglycemia can be made.

Studies have long identified increased QT interval prolongation in patients experiencing a stroke (Burch, Meyers, & Abildskov, 1954; Fukui et al., 2003; Sommargren, Zaroff, Banki, & Drew, 2002), especially with subarachnoid hemorrhage. Like the cardio-renal relationship, the cardio-neuro relationship is not fully understood. Numerous theories have been proposed. One theory is that QT interval prolongation post cerebrovascular accident is due to 'myocardial stunning', possibly due to oxygen derived free radicals and concomitant calcium overload (Bolli & Marban, 1999). Recently Sun et al. (2008) demonstrated an increase in I_{CaL} within an ischemic rat model. This was furthered by Wang et al. (2009) to include reduced function of both I_{Na} and I_{to}. This is the first evidence of ischemia derived cardiac dysfunction.

A related theory is that of excessive release of catecholamine from sympathetic nerve terminals (Zaroff et al., 2006a). Nguyen and Zaroff (2009) explain that catecholamine release from cardiac nerve terminals causes β_1 activation, opening of I_{Ca}, Ca^{2+} influx and cell contraction, leading to depletion of adenosine triphosphate, mitochondrial dysfunction, and eventually cell death. Further research is needed to ascertain the exact pathways causing ventricular repolarization changes post cerebral injury. In our investigation, history of prior stroke independently predicted QT interval prolongation. It may be prudent to provide preventative QT interval monitoring to this patient sample.

Another significant predictor of QT interval prolongation in this investigation was hypothyroid disease. Patients with a history of hypothyroid disease have nearly twice the odds for QT interval prolongation. The mechanism for this relationship, or whether this relationship is truly meaningful, is not currently known; previous studies have been inconclusive. A similar association between QT interval prolongation and thyroid disease was identified in the NHNES III study (Benoit et al., 2005). This association was to patients' self-report of thyroid disease, not specifically hyper- or hypothyroid disease. Other studies have linked QT interval prolongation to both hypothyroidism (Bakiner et al., 2008; Fazio et al., 1992), and hyperthyroidism (Colzani et al., 2001a; C. van Noord et al., 2009). An association between hypothyroidism and QT interval prolongation has also been shown in a canine model (Paslawska et al., 2006), and a guinea pig model (Bosch, Wang, Li, & Nattel, 1999). On the contrary, other studies have found hypothyroidism lead to shorter, not longer, QT interval durations (Asami, Suzuki, Yazaki, Sato, & Uchiyama, 2001; Dorr, Ruppert, Kors, Felix, & Volzke, 2006). Most recently, Abbott and colleagues produced profound hypothyroidism in KCNE2-knockout mice (Roepke et al., 2009). The KCNE2 gene codes for a subunit of the I_{Kr} ion channel and is implicated in CLQTS. Its association with hypothyroidism was not previously known. This reveals a potentially novel endocrine link to cardiac abnormalities (Roepke et al., 2009).

In our investigation we also collected serum TSH. In both univariate and multivariate analysis, elevated serum TSH was not significantly associated with QT interval prolongation. For a possible explanation consider a patient with a history of hypothyroidism receiving drug treatment for correction of thyroid levels. If therapeutic, this patient would have close to normal thyroid function. Therefore serum TSH level will

not correlate with thyroid disease status. Van Noord and colleagues (2008) adjusted for this affect in their study of the Rotterdam sample, and found no relation between serum TSH and QT interval prolongation. Though Dorr et al. (2006) found low serum TSH to be associated with shorter QT interval durations.

Overall, it is not clearly known whether hypo- or hyperthyroid disease causes changes in ventricular repolarization duration. The discovery of KCNE2 gene knockout causing hypothyroidism reveals a previously unknown thyroid-cardio link. Further research is needed to determine these pathways. From our investigation, given its independence for predicting QT interval prolongation, a history of hypothyroid disease should be considered an indication for QT interval monitoring.

Finally, unlike hypothyroid disease, a patient's initial 12 lead electrocardiogram is understandably a significant predictor of developing QT interval prolongation. In this study this was analyzed separately as not all patients had a 12 lead electrocardiogram in their medical record. It was found that the risk for QT interval prolongation was proportional to their initial QT interval group. Patients with an initial QT interval (Bazett's corrected) greater than 441 msecs – 480 msecs had approximately 3 times the odds for QT interval prolongation versus those below 440 msecs, while patients with an initial QT interval greater than 481 msecs had 7 times the odds for QT interval prolongation, adjusting for all other variables. As such, a patient's initial 12 lead electrocardiogram should be taken into consideration when determining whether to provide QT interval monitoring.

Summary

In our investigation female sex, number of proarrhythmic drugs administered, low serum potassium, high serum glucose, high serum creatinine, low serum calcium, history of prior stroke, history of hypothyroid disease, and initial QT interval on 12 lead electrocardiogram, all independently contribute to predicting patients who develop QT interval prolongation. These findings are in line with current literature. However more research, especially in determining how neurological, renal, and thyroid diseases impair ventricular repolarization is needed.

Is QT interval prolongation associated with a) all-cause in-hospital mortality, b) increased length of hospitalization and cardiac monitoring time, c) critical intervention (code blue, medical rapid response), and d) device intervention (pacemaker, interval cardiac defibrillator).

The QT interval has been shown to be an independent predictor for death from all-causes in larger longitudinal studies within diverse samples (Dekker et al., 2004; Robbins et al., 2003; Salles et al., 2009; S. M. Sohaib et al., 2008). Our findings agree. QT interval prolongation is a significant predictor of all-cause mortality, independent of other predictors. These other predictors were: high serum BUN, higher mean heart rate, higher body surface area, history of prior stroke, and number of proarrhythmic drugs administered.

In determining an association with mortality, other studies commonly use 12 lead electrocardiograms with cut-offs for QT interval prolongation ranging from 440 msecs – 470 msecs. In our investigation, 707 patients received a 12 lead electrocardiogram during

their hospital stay. When the automated QTc interval produced from their initial 12 lead electrocardiogram was evaluated with univariate analyses with in-hospital mortality, no relationship was seen. This analysis was performed with the 12 lead electrocardiogram QTc interval as both a continuous variable (alive 429.10 msecs v dead 435.97 msecs, t = - 1.205, *df* 705, p = .229), and a dichotomous variable (mortality with QTc interval > 470 msecs = 5.5% v mortality with QTc interval < 469 msecs = 4.7%, *Fisher's exact value p* = .771). The lack of relationship was sustained when entered into a fully adjusted multivariate model. On post hoc computation of achieved power, given the size and proportions of mortality in each group, this analysis had 6% power to detect a difference, demonstrating that this analysis was grossly underpowered.

When the averaged-mean QT interval from the continuous QT interval monitoring system is evaluated in the same univariate analyses, it was found to be a better predictor of all-cause in-hospital mortality than the automated QTc interval derived from the initial 12 lead electrocardiogram; averaged-mean QT interval as a continuous variable (alive 431.16 msecs v dead 444.12 msecs, t = - 2.214, *df* 992, p = .027), and as a dichotomous variable (mortality with QTc interval > 470 msecs = 10.4% v mortality with QTc interval < 469 msecs = 3.5%, *Fisher's exact value p* = .009).

When this threshold is increased to above 500 msecs, it was *not* associated with all-cause in-hospital mortality (mortality with averaged-mean QT interval > 500 msecs = 6.7% v mortality with averaged-mean QT interval < 499 msecs = 4%, *Fisher's exact value p* = .465). This can be explained in two ways. First undetected patients with depolarization delays (wide QRS complexes) with low co-morbid risk factors are

confounding. Second, and most likely this is a type II error; post hoc computation determines that this analysis was grossly underpowered (power (1-β) = 7.4%).

Overall, our investigation finds that an episode of QT interval prolongation greater than 500 msecs for 15 minutes or longer dichotomized from mean QT interval data, was associated with higher all-cause in-hospital mortality. In post computation, this analysis reached 97% power (1-β) and 3.8% alpha (α). Additionally, in binary logistic regression, QT interval prolongation derived from the continuous QT interval monitoring system remained a significant independent predictor for all-cause in-hospital mortality.

A limitation in our evaluation of QT interval prolongation and its relationship with all-cause in-hospital mortality is failing to collect Acute Physiology, Age, Chronic Health Evaluation (APACHE) scores. These scores are validated predictors of mortality in critically ill patients (Knaus et al., 1991; Zimmerman, Kramer, McNair, & Malila, 2006). In a study by (Burkett et al., 2009) they found that higher heart rate, use of inotropes, high blood glucose level and low serum magnesium independently predicted QTc interval duration, but QTc interval prolongation beyond 440 msecs was not predictive of mortality in a critical care sample; only APACHE II score and mean arterial pressure was. Whether QT interval prolongation, as defined in our investigation, remains an independent predictor of in-hospital all-cause mortality when APACHE scores are included in a fully adjusted model, is a direction for future research.

In addition to mortality, this investigation also finds that QT interval prolongation is a predictor of length of hospitalization, independent to all other variables, and is associated with longer cardiac monitoring time. Patients with QT interval prolongation

had hospital stays on average 6 days longer than those with normal or low QT interval durations, and had on average 77 more hours of cardiac monitoring. Post hoc computation of these analyses, given the sample size, means, and standard deviations of those with and without QT interval prolongation, reveals a power of 99-100%. In a multiple regression model, QT interval prolongation increased hospitalization stay by 3.37 days, independent of all other predictors.

A previous study by Freeman et al. (2008) identified that patients receiving proarrhythmic drugs had significantly longer length of stays in the Intensive Care Unit (13.3 v 8.4 days, $p < .001$). These researchers only counted proarrhythmic drugs if they were administered for greater than 24 hours, possibly biasing the results; one could suggest that only the sickest patients require chronic proarrhythmic drugs. Amiodarone was the most common proarrhythmic drug administered in this study (Freeman et al., 2008). In another study, Chao et al. (2009) found that the QTc interval was a predictor of bed confinement post stroke, independent of age, sex, Glasgow Coma Scale (GCS) score, and National Institutes of Health Stroke Scale (NIHSS). These researchers did not find the QT interval to be an independent predictor of mortality and failed to report total length of hospitalization.

Our finding of increased length of hospitalization is akin to our findings with all-cause in-hospital mortality. Without another measure of patient severity like APACHE score, we cannot determine whether the QT interval is actually a direct predictor of increased monitoring time and hospitalization, or more likely, a reflection of the patient's deteriorating health condition and disturbed cardiac function. Its independence as a

predictor for length of hospital stay and cardiac monitoring duration is a direction for future research.

Finally, we attempted to assess whether QT interval prolongation is associated with the need for critical intervention due to a medical emergency or resuscitation, and also the need for electrophysiology laboratory procedures. On univariate analyses, patients with QT interval prolongation did require more critical intervention than those without QT interval prolongation (7.1% v 2.4%, *Fisher's exact p* = .001, post-hoc α = 3.7, power (1-β) = 91%), however with multivariate modeling this was not significant. Due to the small number of patients with a critical intervention (n = 31), this variable was analyzed as critical interventions from *all-causes* (i.e. respiratory compromise, acute delirium, hypotension). If a larger sample was found with QT interval related critical interventions (i.e. ventricular arrhythmia requiring resuscitation), this subset could be analyzed separately, and hypothetically the relationship between QT interval prolongation and critical intervention would change.

Also on univariate analysis, QT interval prolongation was not associated with electrophysiology laboratory procedures (2.4% v 3.8%, *Fisher's exact value p* =.328). Similarly, the number of patients requiring electrophysiology laboratory procedures was small (n = 36). There was only 1 ablation due to a ventricular tachycardia and on qualitative review this patient did not have an episode of QT interval prolongation. Post hoc computation revealed that this analysis was underpowered to detect a difference in proportions of device intervention (α = 3.6, power (1-β) = 13.6%), if one truly existed between those with and without QT interval prolongation.

Limitations

Investigation of Nurses

-The instrument used in this investigation was developed by the researcher. Though pilot tested, it has not undergone formal psychometric testing to determine construct validity. Face validity was determined with expert oversight. We cannot purport this instrument to be an accurate measure of nurses QT interval knowledge, skills, or abilities.

-Items within this instrument used fixed responses. Therefore by chance, respondents had a 25% probability of a correct response. With this understanding, our data may overestimate the true QT interval related knowledge of nurses within this investigation.

-Within our sample, 77.3% of participating nurses possessed a Bachelor's level of nursing education or higher. The Bureau of Professions (2004) currently estimates that only 30.5% of Registered Nurses possess a Bachelor's degree level of education. With a much greater proportion of nurses with a higher level of nursing education, our study sample may not be representative of the greater sample of nurses. Additionally, as this was only conducted in one institution, mono-operation bias exists.

-Potential unreliability of measures. The education class was administered in small groups at times convenient to participating nurses. The setting was not controlled, nurses could sit were they choose. There was therefore potential for nurses to interact during administration of both pre test and post test. This is a *potential* confounder as no nurses were identified to have collaborated on either test.

Investigation of Patients

-Potential errors in sampling. Full disclosure data obtained from the Philips Intellivue Patient Monitoring System was used to determine the sample of patients admitted to a study unit over the 2 month investigation period. This method of enrollment is dependent upon nurses correctly entering a patient identifier (i.e. medical record number) into the central monitoring station. This was standard nursing practice. It is foreseeable that some patients lacked accurate patient identifiers and were therefore excluded from this investigation. An accurate number of these instances are not known, though it is thought that these cases are small in number and random in occurrence.

-Electrolytes: serum blood variables were collected verbatim from patient's medical record. Depending on the variable, the lowest or highest reported level, regardless of time/day, occurring during the investigation's 2 month period was recorded. As the AHA practice standards (Drew et al., 2004) identify *any* episode of electrolyte disturbance as being an indication for QT interval monitoring, this data collection method suitably classifies patient's serum electrolyte levels for the purpose of this investigation. This methodology has been used previously (Ehret et al., 2006). However, we did not control for many serum related variables: time of day, fasting v non-fasting.

-The continuous monitoring system collects data over the patient's entire length of stay. In this investigation, due to researcher restrictions, analyzing QT interval data over time was not possible. Instead, the patients QT interval data were sorted by maximum mean QT interval values and a dichotomous variable established. This grossly

reduces the level of QT interval specific patient data available in this investigation, and may lead to measurement bias.

-Measurement bias: A unit (CCU) within the investigation switched to an EASI lead system before study commencement. This causes the continuous QT interval monitoring system to average over 12 leads instead of 7 leads; a theoretically advantageous method. Both are products of Philips Medical Systems and utilize the same algorithm for determining QT interval measurements. On post study analysis, CCU had reported higher mean QT intervals than other units, though this was not statistically significant (F = 1.204, df 4,1459, p = .307). Also, CCU had the lowest number of patients with an episode of QT interval prolongation (n = 21). Though unknown, with a robust sample and no significant differences detected, the affect of this lead change is thought to be minimal.

Misclassification biases: Unreliability of measures. All patient demographic and clinical variables were obtained from medical record, verbatim. There is a real possibility that in the course of the patient's hospitalization errors were made. These errors could be introduced into the study and affect analyses when correlated with a physiological marker (QT interval). Clinical data obtained from the medical record was not cross-checked for accuracy.

-Patient data were extracted verbatim from the medical record by a sole researcher. Every effort was made to remove bias/error. At the completion of data collection, variables were sorted and outliers verified. If an error had occurred, these were

rectified on a case by case basis. There is a real potential that non-outlier errors exist within the data. These errors could affect study results.

-Patients on chronic proarrhythmic drugs (i.e. amiodarone) were included in this investigation. This may bias results and inflate the prevalence of QT interval prolongation in the acutely ill sample. Evaluating for this, only 1.5% of the study sample had chronic QT interval prolongation (averaged-mean QT interval greater than 500 msecs). Therefore the effect of these patients remaining in the sample is thought to be minimal.

-Patients medical history was collected verbatim from the medical record. Data were collated as a 'history of …' Classifications for each disease; for example, heart failure classification, types and severity of stroke, degree of renal disease (acute v chronic), type location of myocardial infarction; were not routinely nor reliably documented. Therefore, patients with these diseases were classified under an umbrella term.

Conclusion

This is the first study to evaluate nurses' abilities to perform QT interval monitoring. It was shown that nurses at baseline and after intensive education could not reliably perform QT interval monitoring. This was predominately due to an inability to calculate the QT interval correction formula. As such non-manual methods utilizing semi-automated and/or fully automated methods should be adopted.

Also, this is the only study to date to use the AHA practice standards (an expert consensus document) as they relate to QT interval monitoring to establish the monitoring need and the prevalence and predictors for QT interval prolongation in an acutely ill sample. Our investigation reveals that the AHA indications for QT interval monitoring successfully identify the vast majority of patients developing QT interval prolongation (88.9%), though the positive predictive value was low (31.2%). In using the continuous QT interval monitoring system a low positive predictive value is of little concern. However for clinicians using other QT interval monitoring methods (manual methods), the high degree of difficulty associated with monitoring and the relatively low yield of those with QT interval prolongation is a real concern. Better predictors of QT interval prolongation and methods for monitoring are needed.

Our investigation verifies that female sex, proarrhythmic drugs, and hypokalemia are significant risk factors for QT interval prolongation. We also identify serum glucose above 200 mg/dL, serum creatinine above 1.5 mg/dL, serum calcium below 9 mg/dL, history of hypothyroidism and a prior history for all-types of cerebrovascular accident as additional significant predictors for QT interval prolongation. Literature has previously

suggested that these variables are associated with QT interval prolongation; our findings support these studies and extend them in an acutely ill cohort.

Additionally, we also find that QT interval prolongation is associated with increased all-cause in-hospital mortality, longer monitoring time, and longer hospitalization. Though significant, caution should be taken in interpreting these results. The mechanism linking increased ventricular repolarization and duration of hospitalization or all-cause mortality is difficult to ascertain. Evaluating QT interval prolongation's ability to predict these adverse outcomes should be performed against known predictors of patient severity (i.e. APACHE score). This is an area for future research.

Finally, there are three major strengths in this investigation that should be highlighted. This is the first study to use a continuous QT interval monitoring system. Our analyses are based on over 67,000 hours of QT interval data. Using this system we are able to capture QT interval data from all continuous patients admitted to an adult cardiac monitoring unit over a 2 month period. This is important. The AHA practice standards are aimed at guiding clinician's in-hospital electrocardiographic monitoring practices. Yet the majority of studies assessing prevalence or risk factors for QT interval prolongation are in large community based samples using 10 second 12-lead electrocardiograms. This is the first study to use a continuous QT interval monitoring system in a large acutely ill cohort. In addition to the quantity of data obtained with an important cohort, a rigorous approach was used to identify those with QT interval prolongation. As such, we found that 24% of acutely ill patients had a QT interval that is considered to be dangerously prolonged. Future analysis of this data will be aimed at

determining the electrocardiographic predictors for and the true incidence of TdP in this acutely ill cohort.

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APPENDICES

Appendix A

Nurse Knowledge Test

Demographics.

Age: _____ years Gender: ☐ Male ☐ Female

Years of Nursing Experience:
☐ less than 1 year
☐ 1-3 years
☐ 3-5 years
☐ 5-10 years
☐ 10-15 years
☐ >15 years

Highest Nursing Degree (tick): ☐ Associates ☐Bachelors ☐Masters ☐PhD

Specialty Certification:
☐ CCRN
☐ CEN
☐ Other. Name: _____

Where do you mainly work (tick one only):
☐ Cardiovascular Intensive Care Unit (NICU)
☐ Med/Surg Trauma (E2)
☐ Coronary Care (CCU)
☐ Cardiac Intermediate ICU (B2)
☐ Intermediate ICU (D2/D3-G2S)

Years of nursing experience on a unit providing ECG monitoring:
☐ less than 1 year
☐ 1-3 years
☐ 3-5 years
☐ 5-10 years
☐ 10-15 years
☐ >15 years

Have you ever received formal education on how to use the bedside monitoring system:
☐ No
☐ Yes
☐ Not sure

Section 2.

Please answer all questions.

A lengthened QT interval will place the patient at risk for which arrhythmia? (Circle one)

a) Atrial Flutter
b) Torsades de pointes
c) Wolf-Parkinson-White
d) Ventricular fibrillation
e) Junctional tachycardia

The following are signs of the impending arrhythmia identified above, **except** which one (Circle one)

a) Non-sustained monomorphic VT (unifocal)
b) QT_c interval >0.50sec
c) T wave alternans (every other T wave is taller)
d) New onset polymorphic ventricular ectopy and couplets

What other conditions can result in a prolonged QT interval? (Circle one)

a) Congenital long QT syndrome, severe bradycardias, neurological disorders such as subarachnoid hemorrhage
b) Hypokalemia, hypomagnesia, and Wolff-Parkinson-White Syndrome
c) Congenital long QT syndrome and COPD
d) Renal failure and congestive heart failure

According to the AHA guidelines, how often should the QT interval be documented in a patient receiving cardiac monitoring? (Circle one)

a) When QT-related arrhythmias occur
b) Only with ST elevation
c) When hypokalemia occurs
d) Minimum once per shift, more if QT interval is increasing

Corrected QT intervals show what the interval would be if the heart rate were:

a) 80 bpm
b) 75 bpm
c) 100 bpm
d) 60 bpm

Which patient would be a **'top priority'** for QT interval monitoring (choose one).

a) 50 yr male with hypertension
b) 25 yr female overdosed with unknown medications
c) Elderly female with shortness of breath
d) 75 yr male post cardiac surgery

A patient on a telemetry monitor unit develops an increase in QT_C interval from 0.44 sec to 0.52 sec. The prolonged QT_C interval may not be due to abnormal ventricular repolarization if which of the following conditions has developed?

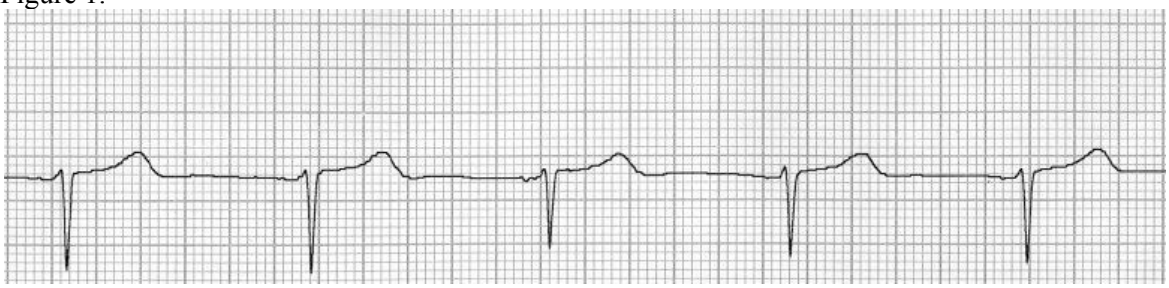
a) Patient has developed renal insufficiency
b) Patient has developed left bundle branch block
c) Patient has no history of congenital long QT syndrome
d) Patient has normal electrolytes

You administer ibutilide (Corvert) intravenously in a patient who presents to the emergency department with palpitations and new onset atrial fibrillation. If this drug causes torsades de pointes, when is it most likely to happen?

a) 4-6 hours following drug administration
b) 6-24 hours following drug administered
c) When the patient converts to sinus rhythm (Typically within 30 mins of drug administration)
d) Can occur anytime during the 72 hours following drug administration

Questions 9-11 refer to the diagram (Figure 1) below.

Figure 1.



By drawing on the rhythm strip above (Figure 1) indicate clearly the **QT interval** of the indicated ECG complex and by drawing on the rhythm strip, indicate the preceding **RR interval**.

Measure the above QT interval in seconds: _____seconds.

Measure the above RR interval in seconds: _____seconds.

Calculate the QTc interval (show working):

END TEST

Appendix B

Operational Definitions for Clinical Data

Variable	Operational Definition
	DEMOGRAPHICS
Age	Calculated variable from date of birth and admission data
Sex	Direct from medical record
Race	Direct from medical record
Hospital unit	Obtained from unique identifier on rhythm data
Body surface area	Initial reported upon admission
Weight	Upon admission in kilograms
Mortality	Electronic record warning of patients demise
Length of stay	Calculated from admission and discharge data – medical record
	CLINICAL MEASURES
Systolic blood pressure	Initial reported upon admission
Diastolic blood pressure	Initial reported upon admission
12 lead electrocardiogram	Initial recorded upon admission
Mean heart rate	Calculated from continuous bedside rhythm data
Mean QTc interval	Direct report from continuous bedside rhythm data
QT interval prolongation	Longer than 500 msecs for 15 minutes from continuous QT system data
Bradycardia	Episode of heart rate below 40 beats per minute obtained from rhythm data
	MEDICAL HISTORY
Heart failure	Any documented in patient history, all types
Myocardial infarction	Any documented in patient history, all types
Coronary artery disease	Any documented in patient history, all types
Cerebrovascular accident	Any documented in patient history, all types
Hypertension	Any documented in patient history
Hyperlipidemia	Any documented in patient history
Diabetes	Any documented in patient history, all types
Renal disease	Any documented in patient history, all types
Liver disease	Any documented in patient history, all types
Depression	Any documented in patient history
Hypothyroid disease	Any documented in patient history
Long qt syndrome	Any documented in patient history, all types
Overdose	Admission record from emergency department
	LABORATORY DATA
Sodium	Lowest recorded: Dichotomized at 135 mmol/L
Chloride	Lowest recorded: Dichotomized at 95 mmol/L
Potassium	Lowest recorded: Dichotomized at 3.5 mmol/L
Calcium	Lowest recorded: Dichotomized at 9 mg/dL
Magnesium	Lowest recorded: Dichotomized at 1.5 mg/dL
Glucose	Highest recorded Categorized: 3 groups (normal <125, mild 125-199, severe >200)
Creatinine	Highest recorded: Dichotomized at 1.5 mg/dL
Blood urea nitrogen	Same time as creatinine value: Dichotomized at 25 mg/dL
Thyroid stimulating hormone	Any recorded: Dichotomized at 5.5 uIU/ml
	TREATMENT RELATED
Proarrhythmic drug admin.	Dichotomized from medication administration record (MAR)
Ejection Fraction	Echocardiography data (severe <36%, mild 36-49%, normal >50%)
Critical intervention	Dichotomized from rapid response, code blue team documentation
Device intervention	Dichotomized from EP procedural list

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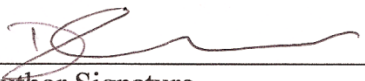

Author Signature

1-8-10

Date