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Review Article

Fatal Drowning Associated with QT Prolongation Caused by Alcohol, Some Drugs, and Congenital Long QT Syndrome: The Role of the Diving Reflex

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Abstract

Fatal drowning is a common cause of death, particularly among young persons. Most swimming-related deaths are caused by arrhythmias. The diving reflex increases both sympathetic and parasympathetic tone to the heart causing increased ventricular automaticity and bradycardia, respectively. Bradycardia increases the risk of Torsade de Pointes and sudden cardiac death when the QT interval is prolonged. Congenital long QT syndrome is clearly associated with drowning. Alcohol and some QT-prolonging drugs are also associated with drowning, but documentation is limited because forensic toxicology is seldom performed on postmortem blood of drowning victims. Hypokalemia also causes long QT and by inference is associated with fatal drowning although postmortem evidence is lacking. Bradycardia of the dive reflex coupled with long QT and ventricular extrasystoles increases the risk of sudden cardiac death in the water - a death typically classified as a fatal drowning. Irrespective of the underlying cause(s) of QT prolongation, bradycardia of the diving reflex increases the risk of fatal drowning. Many drugs, including alcohol, prolong the QT interval. Although not yet widely appreciated, the risk of fatal consequences from QT-prolonging drugs is increased by the dive reflex.

Keywords: *Alcohol; Hyperventilation; Hypokalemia; Long QT Syndrome; Sudden Cardiac Death; Swimming*

Abbreviations

BAC: Blood Alcohol Concentration; CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia; DILQTS: Drug-induced Long QT Syndrome; ECG: Electrocardiogram; FDA: United States Food and Drug Administration; LQTS: Congenital Long QT Syndrome; NCAA: National Collegiate Athletic Association; PM: Postmortem; QT: QT Interval of the Electrocardiogram; QTc: QT Corrected for Heart Rate; QTd; QT Dispersion; SCD: Sudden Cardiac Death; SSRI: Selective Serotonin Reuptake Inhibitor; TdP: Torsade de Pointes; VF: Ventricular Fibrillation; WHO: World Health Organization

Introduction

The WARNINGS section of United States Food and Drug Administration (FDA)-approved labeling for the antidepressant drug Celexa® (citalopram hydrobromide, Forest Pharmaceuticals, Inc., Subsidiary of Forest Laboratories, Inc., St. Louis, MO 63045 USA) includes in part: "Citalopram causes dose-dependent QTc prolongation, an ECG abnormality that has been associated with Torsade de Pointes (TdP), ventricular tachycardia, and sudden death, all of which have been observed in post-marketing reports for citalopram. It is recommended that citalopram should not be used in patients with congenital long QT syndrome, bradycardia, hypokalemia or hypomagnesemia, recent myocardial infarction, or uncompensated heart failure. Citalopram should also not be used in patients who are taking other drugs that prolong the QTc interval" [1].

The conditions listed above may arise among patients or potential patients of Celexa®, and yet the basis for such warnings may not be apparent to the average prescriber. For example, what is it about bradycardia that militates against the usage of citalopram? As will become evident below, the same question needs to be posed for any of approximately 200 QT-prolonging drugs listed by Credible Meds [2] as well as for other QT-prolonging influences. Bradycardia happens during swimming and other water-related activities because of the mammalian dive reflex [3-7]. During the dive response, sympathetic outflow to heart and peripheral blood vessels is also increased. Blood is shunted to heart and brain. Simultaneous activation of parasympathetic outflow to the heart inhibits pacemaker cells of the sino-atrial node, an effect that dominates over sympathetic stimulation. Thus bradycardia normally occurs during the dive response [4,5,7]. This review will explore the mechanisms and links between drug and/or otherwise prolonged QT, bradycardia, and sudden cardiac death (SCD) in water – deaths typically classified as a fatal drowning.

Recreational or competitive swimming is enjoyed by many individuals even when it is recognized that there is a small but finite risk of fatal drowning. Inadvertent immersion or submersion in a body of water may also lead to a fatal outcome. Drowning is a major cause of traumatic death and is the fifth leading cause of unintentional death in the United States [8] and over 300,000 fatal drownings per year worldwide [9].

In 2005 the World Health Organization (WHO) adopted the definition of drowning as, "The process of experiencing respiratory impairment due to submersion or immersion in liquid" [10]. The definition does not specify the outcome. Thus, drowning can be classified as having been 'fatal,' 'non-fatal,' or 'with morbidity.' Previously used modifiers such as 'near,' 'wet,' or 'dry' are no longer recommended [11]. While the WHO definition is based on respiratory impairment, a recent review concluded that cardiac arrhythmias are the most likely cause of swimming-related death among athletes [12]. Thus, whether death occurs during competitive, recreational or unintentional immersion/submersion in water, fatal drowning is often initially due to SCD.

Prolongation of the QT interval (QT) of the electrocardiogram is a critical key in many cases of fatal drowning. When combined with the bradycardia of the mammalian dive reflex, prolonged QT increases the risk of SCD – a death that occurs in water and is thus typically classified as a fatal drowning. The current communication draws evidence from diverse sources to consider multiple factors that prolong QT and to make sense of how such factors contribute to fatal arrhythmias in water.

The QT interval

Excellent articles on the normal determinants of QT are available [13-16]. If the rate-corrected QT (QTc) is > 450 ms for males and > 470 ms for females, then it is considered to be prolonged [17]. Repolarization of the epicardium coincides with the peak of the T wave while repolarization of the deep subendocardium-midmyocardium, the last to repolarize, coincides with the end of the T wave [14]. The time between the peak of the T wave and the end of the T wave is an index of transmural dispersion of repolarization, which is the fundamental problem in reentry excitation and potentially fatal sequelae [18,19].

Many different genetic mutations and altered cardiac ion channel functions are associated with a variety of congenital long QT syndrome (LQTS) types [20-22]. Patients with LQTS may suffer from syncope, or rarely, SCD early in life [23], but many individuals lead normal lives and have no signs or symptoms. Prolonged QTc is an independent risk factor for SCD in older adults with an estimated relative risk of 8.0 for patients with 55 - 68 years of age [24]. QTc-prolonging drugs increase the risk of SCD with an odds ratio of 2.7 (95% CI: 1.6 - 4.7) [25]

Autonomic reflexes activated by water, particularly cold water, can increase the risk of SCD [26,27]. As discussed below, the risk of SCD in water is further increased when long QT is coupled with the bradycardia of the mammalian diving reflex. Evidence for this mechanism comes mainly from case reports and studies involving relatively small numbers of subjects or victims. Some studies included postmortem (PM) genetic analyses of congenital long QT syndrome. Some examined the QT-prolonging effects of a variety of seemingly unrelated drugs or medical conditions. Others described the potential arrhythmic effects of the diving reflex. The common thread that links evidence scattered among apparently diverse publications is QT prolongation, its interaction with bradycardia of the dive reflex, and the resultant increase in the risk of SCD in water.

The mammalian dive reflex

The mammalian dive reflex, also known as the diving reflex or dive response, evolved because it conserves oxygen when the body is immersed in water. As noted by Lazar*., et al.,* increased venous return that occurs as a consequence of immersion or submersion in water results in increased parasympathetic tone and bradycardia [6]. Facial cold [7] or facial immersion in the absence of bodily immersion also promotes increased parasympathetic tone and bradycardia [3-5]. During the dive response, sympathetic outflow to heart and peripheral blood vessels is also increased. Blood is shunted to heart and brain. Simultaneous activation of parasympathetic outflow to the heart inhibits pacemaker cells of the sino-atrial node, an effect that dominates over sympathetic stimulation. Thus bradycardia normally occurs during the dive response [4,5,7].

The dive response itself does not prolong QT [28,29], but AV block, P wave flattening, PR prolongation, abnormal atrial activation, AV block, and junctional beats are observed [28]. Abnormal rhythms occur particularly at the nadir of heart rate during face immersion in water of different temperatures from warm to cold [28]. Autonomic responses are greater during simultaneous facial cold and apnea than with facial cold or apnea alone [7]. Activation of both divisions of the autonomic nervous system, particularly during cold-water immersion, prompted Shattock and Tipton to attribute resultant arrhythmias to 'autonomic conflict' [26]. Vagal effects on the sino-atrial node coupled with enhanced sympathetic influences on the ventricular myocardium facilitate the production of arrhythmias [30].

Arrhythmias

If an ectopic beat arises in the ventricle when QT is prolonged, then it is more likely to occur in the so-called 'vulnerable period' and possibly trigger reentry excitation, Torsade de Pointes (TdP), ventricular fibrillation (VF) and SCD [19]. Bradycardia of the dive reflex was recognized as a possible contributor to SCD [31]. Of course, the likelihood of ectopic ventricular beats increases during bradycardia. While a variety of mechanisms may trigger or otherwise facilitate abnormal rhythms, once such rhythms are initiated the risk of a fatal outcome increases.

Dysrhythmias triggered by immersion bradycardia were deemed to be among fatal mechanisms in snorkeling deaths in Australia, particularly among elderly victims many, but not all of whom had a pre-existing cardiac condition [32]. Although not specified, it is likely that some of the snorkeling victims had taken alcohol and/or drugs.

Even in the absence of swimming-induced triggering of arrhythmias, QT prolongation is a significant risk for the development of TdP and SCD [33]. Hypokalemia, drug-induced long QT syndrome (DILQTS) [34], and LQTS are each pro-arrhythmic and are presumably at least additive if not synergistic in promoting SCD [19,24,25,35-37]. In water, any one or a combination of such factors may lead to SCD classified as a fatal drowning.

Figure 1 depicts several categories of QT-prolonging premortem influences that when combined with the dive reflex, increase the risk of SCD in water. Such influences may include 1) metabolic, including electrolyte, abnormalities that are difficult to establish by PM analysis, 2) alcohol or other QT-prolonging drugs that have been taken acutely or chronically - the presence of which will be established only if appropriate forensic toxicology is performed on the PM blood and, 3) congenital LQTS that can be confirmed by PM genetic analysis.

Metabolic abnormalities

Metabolic, abnormalities, particularly electrolyte imbalances, may cause QT prolongation [38], but there is little definitive evidence regarding metabolic abnormalities and fatal drowning. Death by drowning will obscure premortem abnormalities such as hypokalemia. Hypokalemia was found to be the strongest non-cardiologic factor associated with QT prolongation in an emergency department [37]. A systematic review aimed at assessing the association between QTc and risk factors for TdP and SCD found very strong evidence for hypokalemia and for the drugs categorized by CredibleMeds [2] as having a known risk of TdP [39]. The systematic review included only observational studies with 500 or more patients from a general population but none involving drowning. While useful in identifying possible risk factors for QT prolongation per se, possible association with drowning was not considered in these studies [37,39].

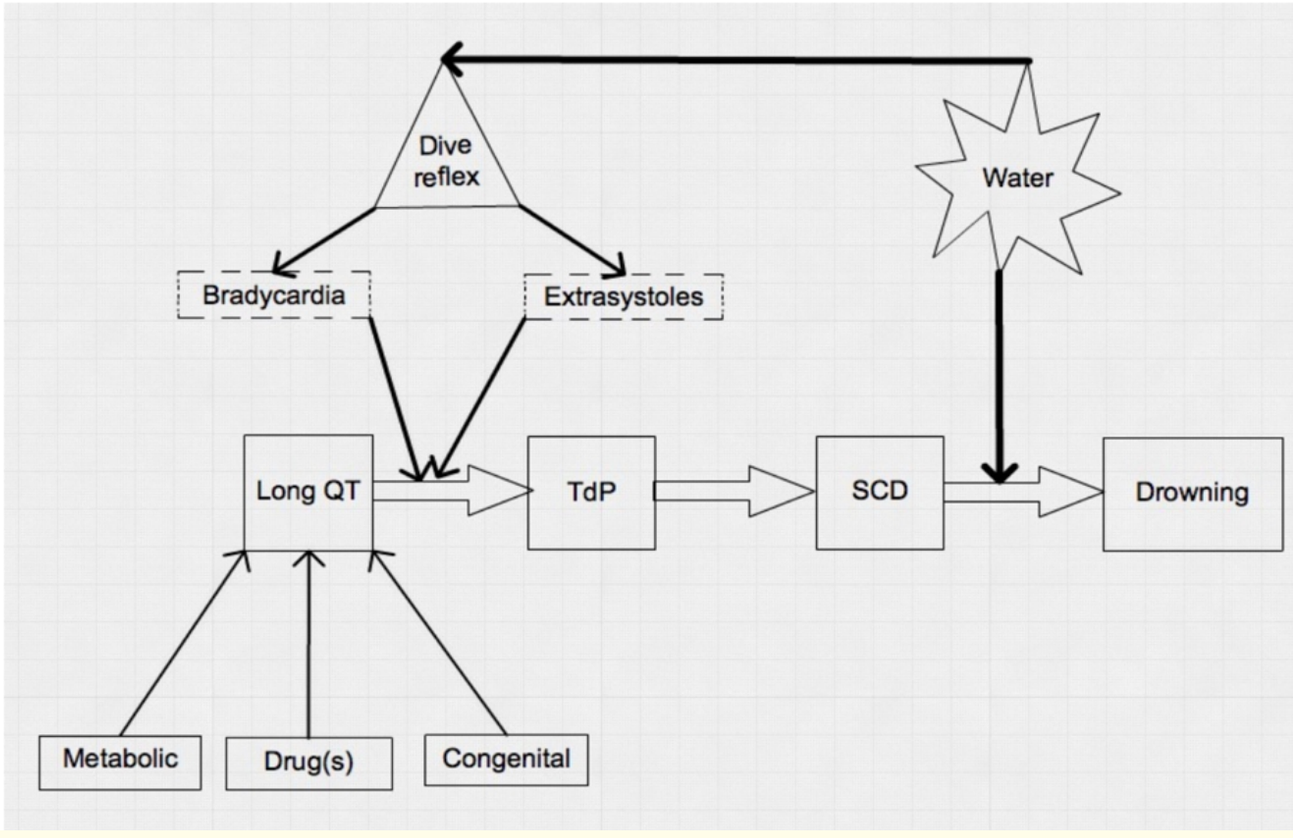

Figure 1: *Simplified diagram of long QT and fatal drowning. The QT interval may be increased by one or more factors: 1) metabolic (e.g. hypokalemia), 2) alcohol or drug(s), 3) congenitally. Non-symptomatic prolongation of the QT interval may exist for long periods of time without incident. When the dive reflex is activated in water increased sympathetic tone increases the likelihood of ventricular extrasystoles. Simultaneously, increased parasympathetic tone causes bradycardia. In such circumstances, long QT increases the risk of Torsade de Pointes (TdP) and ventricular fibrillation resulting in sudden cardiac death (SCD) in water – a fatal drowning.*

Pearn., et al. [40] noted that the differential diagnoses of sudden unexpected death of a swimmer include 1) coronary disease or cardiomyopathy, 2) preexistent cardiac conduction abnormalities, 3) epilepsy, 4) hypoxic blackout. Hypoxic blackout, also known as shallow water blackout, is a sudden loss of consciousness during a breath-holding dive following hyperventilation [41]. The outcome is usually fatal and occurs most often in young males [40]. Of course, hyperventilation rapidly decreases carbon dioxide in the blood with a concomitant increase in pH. Hyperventilation also causes potentially arrhythmogenic hypokalemia almost immediately [42] and QT prolongation within a minute [43].

The generally accepted explanation of hypoxic blackout is that, during breath-holding under water, carbon dioxide does not accumulate to a level sufficient to stimulate the urge to surface and breathe. At the same time, oxygen is consumed to such a low level that consciousness is suddenly lost under water. In a review of hypoxic blackout, Pearn., *et al.* [40] cite a personal communication of Tipton. Tipton hypothesized that hyperventilation might trigger autonomic conflict [26] and thus contribute to sudden death in the water. As noted above, even a short period of hyperventilation causes hypokalemia [42] and QT prolongation [43]. One may speculate that transient hypokalemia and QT prolongation caused by hyperventilation when combined with the bradycardia of the dive reflex, increases the risk of sudden unexpected death among breath-holding swimmers. Pearn., et al. suggested that during aquatic misadventure related to cardiac causes (e.g. LQTS) the swimmer is typically seen on the surface having stopped swimming and exhibiting peculiar behavior for a few seconds [40]. By contrast, the swimmer that experienced hypoxic blackout is typically found unconscious or dead at the bottom of the body of water without having surfaced [40]. If hyperventilation-induced long QT and autonomic conflict were to result in the sudden underwater onset of VF, then the death would appear to have been caused by hypoxic blackout. However, the brain hypoxia would be related to a lack

of delivery of oxygen, rather than to hypoxemia. In such a case, indistinguishable at autopsy from 'classical' hypoxic blackout, the transient metabolic abnormality of hyperventilation-induced hypokalemia [42] and QT prolongation [43] combined with the autonomic conflict and bradycardia of the dive reflex [26], triggers the sudden onset of a fatal arrhythmia. Further research is needed on this question.

QT-prolonging drugs

CredibleMeds lists more than 200 QT-prolonging drugs [2]. Many such drugs are neither 'drugs of abuse,' nor 'performance-enhancing drugs,' and thus might be in use by an athlete during competition or recreational exercise. Non-athletes use a wide variety of recreational and prescribed drugs in various sport or exercise situations, including swimming.

Alcohol is the drug most commonly associated with fatal drowning [44-50]. Alcohol increases the relative risk of death among recreational boaters, at BAC levels as low as 10 mg/dL with an odds ratio of 52 at a BAC of 250 mg/dL [46].

It is generally assumed that psychomotor impairment is responsible for the association of alcohol with fatal drowning. What is not yet widely appreciated is that alcohol, even at relatively low levels, causes prolonged QT and increased QTd [51, 52]. In a 24-year epidemiological analysis of alcohol and death by drowning in Australia [53], none of the women, but 35% of the men had blood alcohol concentrations (BACs) > 80 mg/dL. One case mentioned by Plueckhahn almost certainly represents alcohol-related SCD in water. A 37-year old excellent swimmer in waist high surf suddenly did not surface and was almost immediately pulled from the water. There was no evidence of heart disease, but his PM BAC was 183 mg/dL [53].

In water, the acute effects of alcohol represent a 'triple threat': psychomotor impairment, QT prolongation, and augmented sympathetic effects of the dive reflex. Psychomotor effects include impairment of both cognitive and motor functions. Impairment of perception and judgment occurs at low BACs well below 100 mg/dL [54,55]. High concentrations of alcohol produce impaired muscular coordination, QT prolongation, and increased risks of arrhythmias [54,55]. In Finland, one of the few countries where forensic toxicology is routinely performed on the PM blood of fatal drowning victims, alcohol was present at ≥ 50 mg/dL in 74.5% of males and 67.4% of females who died in non-boating-related drowning [47]. Among nearly 1700 fatal drowning cases in Finland, 79.6% of victims had a BAC >149 mg/dL [50], well above concentrations at which alcohol prolongs QT and increases QTd [51,52].

Alcohol increases the sympathetic component of the dive reflex as elicited by cold water facial immersion [56]. Particularly in the context of competitive swimming [27], the sympathetic component of the diving reflex as well as the cold shock response [26], may trigger rapid rhythms such as catecholaminergic polymorphic ventricular tachycardia (CPVT). It seems likely that a CPVT-like rhythm due to excessive sympathetic tone is responsible for SCD among some autopsy-negative male basketball players of the National Collegiate Athletic Association (NCAA) athletes. Basketball is the sport most commonly associated with SCD of male athletes, most of whom died during exertion [57]. In such cases, it is unlikely that bradycardia is the trigger of the fatal rhythm as it is among most swimmers who experience SCD in water.

Genetic variants associated with fatal drowning include some that underlie excessive responsiveness to catecholamines [58,59]. Likewise, sympathomimetic drugs such as methamphetamine increase ventricular automaticity and increase the likelihood of CPVT-like rhythms. The risk of such rhythms would be further increased when combined with dose-dependent QT prolongation caused by methamphetamine [60]. The use of sympathomimetic drugs prior to any water activity would appear to be unwise.

QT-prolonging drugs, with or without alcohol, were present in most of the nearly 1700 cases of unintentional fatal drowning reported recently [50]. Second to alcohol, benzodiazepines were among the drugs appearing in the PM blood of unintentional fatal drowning victims; commonly in combination with alcohol or other drugs [50]. Benzodiazepines are not QT-prolonging [2] and when present alone, presumably promote fatal drowning mainly by impairing psychomotor functions.

In contrast to benzodiazepines, many medically prescribed drugs increase QT [33,61-65]. Prominent among the prescription drugs present in the PM blood of fatal drowning victims in the Finnish study were citalopram (a selective serotonin reuptake inhibitor) and amitriptyline (a tricyclic antidepressant) [50]. Neither of these chemically unrelated drugs is notable for causing psychomotor impairment, but each is known to prolong QT [2].

More than other SSRIs, citalopram dose-dependently prolongs QT [65,66] and causes TdP [2]. found no cases of citalopram-induced sudden cardiac death among patients taking up to 60 mg/day and *free of risk factors for QTc prolongation and torsade de pointes*" [emphasis added] [67]. While that may be true, bradycardia of the dive reflex *is* a significant risk factor for QT prolongation and TdP. Apparent TdP and SCD of a patient while SCUBA diving was reported. The patient survived 60 mg/day of citalopram (higher than the recommended dosage) for more than a year until she went diving [68].

Many QT-prolonging psychotropic drugs, such as citalopram, are widely prescribed and are typically taken chronically. Therefore, they are likely to appear, as in the recent study from Finland, when forensic toxicology is performed on the PM blood of fatal drowning victims [50]. The frequent presence of the self-prescribed QT-prolonging drug, alcohol, has resulted in its well-established association with fatal drowning. Antihistamines, antibiotics, anticancer, antiemetic, and many other prescription drugs increase the risk of TdP [2], but they are seldom identified and rarely quantified in the PM blood of victims of fatal drowning. Furthermore, because so many diverse drug types promote QT prolongation, their connection to fatal drowning has not been apparent.

Consider Zagam® (sparfloxacin, Bertek Pharmaceuticals Inc., Research Triangle Park, NC 27709-4149), an antibiotic which causes a 40% increase in QT [35]. The CONTRAINDICATIONS section states of the FDA-approved labeling for Zagam® states: "Sparfloxacin is contraindicated in patients with known QTc prolongation or in patients being treated concomitantly with medications known to produce an increase in the QTc interval and/or torsade de pointes (e.g. terfenadine). See WARNINGS and PRECAUTIONS." The PRECAUTIONS section indicates that: "Sparfloxacin is not recommended for use in patients with pro-arrhythmic conditions (e.g. hypokalemia, significant bradycardia, congestive heart failure, myocardial ischemia and atrial fibrillation)" [69].

When prescribing Sparfloxacin, it seems unlikely that a health care provider will caution the patient to avoid water-related activities because the dive reflex causes 'significant bradycardia'. In any case, sparfloxacin is not likely to be present in many individuals at risk of drowning because it is given for only a few days. If sparfloxacin were to contribute to fatal drowning in, say, 50% of patients who go swimming, the number of victims would be few and the problem, so to speak, would appear to be small or non-existent. If sparfloxacin were identified in PM blood, its possible contribution to fatal drowning would probably not even be considered. If reported in the literature, it would be a case report. Case reports are considered to represent the lowest level of evidence in medical literature. And yet, as was pointed out recently [70], case reports are important catalysts for identifying hitherto unrecognized adverse drug reactions. Case reports have identified unique situations of patients that increase the risk of adverse outcomes. The simultaneous presence of prolonged QT and bradycardia of the diving reflex is a unique and potentially deadly situation.

Congenital Long QT Syndrome (LQTS)

An early case report provided initial insights into the link between QT prolongation and fatal drowning. Thus, familial association with fatal drowning was reported even before genetic analysis was available [38]. The fact that LQTS increases the risk of fatal drowning was subsequently made abundantly clear by genetic analyses [13,20,58,71-73]. About one in 2000 infants have LQTS [74]. By contrast, nearly thirty percent of unexplained fatal drowning victims had a cardiac ion channel mutation [73]. Ackerman and co-workers suggested that swimming is a gene-specific arrhythmic trigger for persons with the common LQTS mutation, KVLQT1 [71]. Other LQTS mutations were implicated, as were mutations that increased the risk of CPVT [58,59].

A wide variety of allelic variants in long QT genes are associated with drug-induced TdP [16,72]. Various types of inherited channelopathies may be differentially sensitive to the QT-prolonging effects of drugs when a particular combination of metabolic, drug and factors interacts with the dive reflex. Lazar., *et al*. [6] concluded that patients with a history of LQTS should avoid swimming, particularly if there has been genetic verification. But many individuals with various channelopathies have no overt medical history and no genetic analysis. It seems likely that some young individuals who tried swimming as a sport chose not to continue because of a negative subjective experience. Palpitations while swimming [73] of a relative of an LQTS fatal drowning victim might have been a subjectively negative 'near miss' arrhythmia. To an unknown extent, individuals with LQTS self-select out of sports or have been excluded as a consequence of pre-participation examinations. Harmon., *et al.* reported that only 1% SCDs of NCAA athletes were associated with Long QT [57]. In their study, most drownings were classified as 'accidents,' and it is uncertain how many drownings may have been associated with fatal arrhythmias. Maron., *et al.* reported on sudden death among athletes who participated in various sports [75]. The overall incidence of clinically diagnosed LQTS was 7% among females vs. 1.5% among males. Among athletes who participated in swimming/water polo, 8% of females experienced sudden death while only 2% of males experienced sudden death.

Among competitive athletes, ECG screening by physicians is more sensitive and specific for identification of potentially lethal cardiovascular conditions than history and physical [76]. Presumably the same is true among recreational athletes. Uniform postmortem analysis has been strongly urged for investigation of sudden cardiac arrest/SCD among competitive or recreational participants. This should include autopsy (preferably by a cardiac pathologist) as well as molecular autopsy (possible genetic issues) and forensic toxicology (possible drugs of abuse or performance enhancing drugs) [77]. Such uniform analysis needs to be applied to both competitive and recreational victims of fatal drowning to avoid the natural conclusion that they simply had an accident. If such uniform analyses are performed, it is predicted that previously under-appreciated QT prolonging factors will be identified.

Conclusion

Table 1 summarizes evidence that, when combined with the bradycardia of the diving reflex, long QT increases the risk of arrhythmias and SCD in water - fatal drowning. Table 1 also illustrates limitations in the evidence. Hypokalemia is a major cause of QT prolongation [37]. However, proving at autopsy that hypokalemia or non-congenital long QT pre-existed in a fatal drowning victim is virtually impossible. Thus, published evidence that QT prolongation caused by metabolic or electrolyte abnormalities contribute to fatal drowning is almost non-existent. Similar limitations apply to other metabolic or electrolyte abnormalities. Therefore, it is by inference that electrolyte-induced long QT contributes to fatal drowning, including some cases of an apparent hypoxic blackout.

1st Author	Yr	Ref #	CR†	Metabolic	Alcohol	Drug	Congenital
Plueckhahn	1984	43			X		
Harris	1992	36	X				X
Lunetta	1998	44			X		
Ackerman	1999	69					X
Smith	2001	45			X		
Choi	2004	57					X¶
Driscoll	2004	47			X		
Craig	1976	40		X ‡			
Tester	2011	71					X ¶
Lippman	2012	30		X‡			
Ahlm	2013	48			X	X§	
Lazar	2013	21					X
Vincenzi	2015	67	X			X	
Pajunen	2017	49			X	X	

Table 1: *Causes of QT prolongation linked to fatal drowning.*

† Case Report ;‡ QT prolongation by hyperventilation is suggested but needs further investigation.

§ Drugs were identified but not quantified; ¶ Included LQTS and CPVT

By contrast, it is well documented that alcohol has contributed to many fatal drownings. Among its many effects, QT prolongation by alcohol is an almost certain contributor to SCD in water.

Drowning associated with other drugs is less well documented. Drugs are less commonly present than alcohol and, complicating the picture, are often present along with alcohol. Many different types of drugs present alone or with alcohol, make their possible contributions less apparent. It is concluded, as recently hypothesized, that DILQTS contributes to fatal drownings [34]. It is predicted that routine pursuit of forensic evidence will demonstrate that prescription drugs contribute to more fatal drownings than is currently appreciated.

Genetic analysis has identified hundreds of polymorphisms associated with LQTS and an increased risk of SCD [13,20,23]. The link of LQTS (and CPVT) to fatal drowning was amply documented by Ackerman and his co-workers. Their work showed a definite linkage between congenitally-determined QT prolongation and unexplained fatal drowning. This insight provided the initial framework for understanding that when combined with the bradycardia of the diving reflex, and irrespective of the cause(s), QT prolongation is a risk factor for arrhythmias and fatal drowning.

Although for simplicity, metabolic, alcohol, drug and genetic factors were considered separately in the current review, it is clear that any or all such factors may determine the outcome of encounters with water. This is particularly true for cold water [26] during recreational or competitive swimming [27] as well as breath-holding diving following hyperventilation [40]. It is also clear that individuals with congenital LQTS [73], or who have allelic variants that make them particularly sensitive to QT-prolonging drugs [16,72] should avoid water-related activities.

Even without such genetic particularities, individuals who have consumed QT-prolonging doses of alcohol [51,52] and/or other QT-prolonging drugs [2] are at risk of a fatal arrhythmia – a risk that is further increased when the dive reflex is activated. When the common thread of QT prolongation from various causes is recognized, and its interaction with the dive reflex is appreciated, then the contribution of arrhythmias to fatal drowning will be more widely recognized and better understood.

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Author Contributions

Frank F. Vincenzi conceived of this review, searched and interpreted the literature and wrote and approved of the version to be published. There was no outside source of funding.

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Consent for Publication Declaration

Not applicable.

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