Gut and Liver
https://doi.org/10.5009/gnl210537
pISSN 1976-2283 eISSN 2005-1212

Review Article

Prolonged QT Interval in Cirrhosis: Twisting Time?

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Article Info
Received November 19, 2021
Accepted December 7, 2021
Published online July 22, 2022

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Approximately 30% to 70% of patients with cirrhosis have QT interval prolongation. In patients without cirrhosis, QT prolongation is associated with an increased risk of ventricular arrhythmias, such as torsade de pointes (TdP). In cirrhotic patients, there is likely a significant association between the corrected QT (QTc) interval and the severity of liver disease, and possibly with increased mortality. We present a stepwise overview of the pathophysiology and management of acquired long QT syndrome in cirrhosis. The QT interval is mainly determined by ventricular repolarization. To compare the QT interval in time it should be corrected for heart rate (QTc), preferably by the Fridericia method. A QTc interval >450 ms in males and >470 ms in females is considered prolonged. The pathophysiological mechanism remains incompletely understood, but may include metabolic, autonomic or hormonal imbalances, cirrhotic heart failure and/or genetic predisposition. Additional external risk factors for QTc prolongation include medication (I_{Kr} blockade and altered cytochrome P450 activity), bradycardia, electrolyte abnormalities, underlying cardiomyopathy and acute illness. In patients with cirrhosis, multiple hits and cardiac-hepatic interactions are often required to sufficiently erode the repolarization reserve before long QT syndrome and TdP can occur. While some risk factors are unavoidable, overall risk can be mitigated by electrocardiogram monitoring and avoiding drug interactions and electrolyte and acid-base disturbances. In cirrhotic patients with prolonged QTc interval, a joint effort by cardiologists and hepatologists may be useful and significantly improve the clinical course and outcome. **(Gut Liver 2022;16:849-860)**

Key Words: Acquired long QT syndrome; Torsade de pointes; Cirrhosis; Drug interaction; Ventricular repolarization

Round and round and up and down we go again
Do you remember when things were really hummin'?
Let's twist again, twisting time is here

"Let's Twist Again,"[1] sung by Chubby Checker, 1961

INTRODUCTION

The prevalence of electrocardiographic QT interval prolongation in patients with cirrhosis ranges between 30% and 70%.[2,3] In fact, the seminal paper by Kowalski and Abelmann[4] that launched the modern era of cardio-hepatology in 1953 already reported a prolonged QT interval in eight of the 22 subjects. Unfortunately, it was merely an incidental finding that was not further discussed, as the main point of the paper was the demonstration of hyperdynamic circulation in cirrhosis. This phenomenon then remained ignored until 1998, when Bernardi *et al.*[5] performed a detailed study of QT prolongation in cirrhosis and found a significant correlation between the rate-corrected QT (QTc) interval and the Child-Pugh score, and that QTc prolongation may be associated with poor outcomes including mortality.[5] Since then hundreds of studies of repolarization in cirrhosis have appeared. Despite these efforts, the underlying pathophysiology of QT prolongation in

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cirrhosis is poorly understood. Proposed mechanisms such as bile salt accumulation, altered autonomic tone, shifts in gonadal hormone balance and cirrhotic cardiomyopathy have been suggested.

The QTc interval can easily be obtained from a 12-lead electrocardiogram (ECG). Hence, it is easily accessible as 12-lead ECGs are noninvasive, simple, inexpensive and routinely done in hospitalized and ambulatory patients to detect a long QT syndrome (LQTS). LQTS can be classified as either due to genetic mutations, also called the congenital LQTS, or as acquired LQTS where cardiac ion channel function is influenced by extrinsic factors. Patients with a prolonged QTc interval are considered at risk of developing the dreaded torsade de pointes (twisting of the points, TdP) ventricular arrhythmia. In many respects the frenetic up and down, twisting-around motion of the waveform is the electrophysiological equivalent of the "twist" dance craze popularized 6 decades ago. Unfortunately, the outcome of the cardiac twist is considerably more somber than the popular dance as it degenerates into ventricular fibrillation and potentially sudden cardiac death about 20% of the time.[6] As such, much attention is paid to monitoring the QTc interval, particularly when using medications with potential QT prolonging properties. This can significantly affect clinical decisions since certain hepatic pathologies and/or treatments can further impact the QT interval and may reduce pharmacological treatment options in cirrhotic patients with LQTS.

Despite the mountain of available literature, several key questions remain unsettled. The purpose of this review is to discuss the pathogenic mechanisms and translational significance of prolonged QT intervals in cirrhosis from the dual viewpoints of cardiac electrophysiology and hepatology. The literature search strategy of this narrative review was by selective PubMed searches of papers over the past 3 decades under the search terms "QT interval," "QT prolongation," "prolonged QT," "ventricular repolarization," and "cirrhosis." Papers on repolarization and LQTS in the noncirrhotic cardiovascular population were selected based on personal knowledge of the literature by the three cardiac electrophysiologist authors.

THE QT INTERVAL

The QT interval on the ECG represents the total sum of ventricular myocardium action potentials and is defined as the time interval between the start of depolarization and the end of repolarization of the ventricular myocardium (Fig. 1).[7]

To understand the pathophysiology of QT prolongation, a basic knowledge of the ventricular action potential and its most dominant ion channels is crucial (Fig. 1). The action potential starts with a rapid depolarization, phase 0, mediated by voltage gated sodium channels (I_{Na}). In phase 1, the voltage gated sodium channels close and a transient outward current (I_{to}) mediated by voltage gated potassium channels initiates repolarization and a stable outward potassium current I_{Kur} lasting from phase 1 until the end of phase 3 is initiated. The plateau phase or phase 2 allows contraction of the cardiomyocytes and is an equilibrium between an inward calcium current by L-type calcium channels and an outward potassium current (I_{Kur} and I_{Ks}). The repolarization is continued to baseline in phase 3 as the L-type calcium channels close, and outward potassium currents continue with I_{Ks} and I_{Kr}. In phase 4 the membrane voltage will be maintained mainly by potassium channels (I_{K1} and I_{KATP}). Hence, when discussing the ventricular repolarization or the QT interval, the L-type calcium and outward potassium currents I_{Ks} and I_{Kr} are most important.

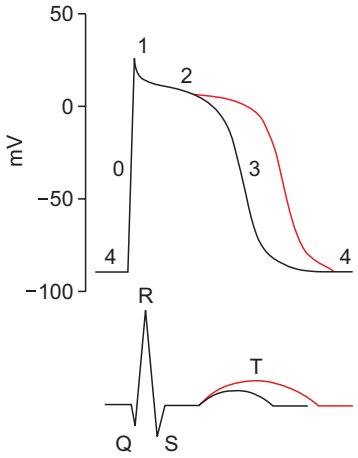

Fig. 1. Action potential of ventricular myocardium and corresponding electrocardiogram (ECG). Example of a normal ventricular myocardial action potential with normal QT interval (black line) and a prolonged ventricular action potential due to I_{Kr} block resulting in a prolonged phase 2 and 3 of the action potential and prolonged QT interval (red line). Phase 0: rapid depolarization mediated by voltage gated sodium channels (I_{Na}) corresponding with the start of the QRS complex on the ECG. Phase 1: closure of the sodium channels. Short transient outward current (I_{to}) mediated by voltage gated potassium channels. Phase 2: plateau phase by an equilibrium between the inward calcium current by L-type calcium channels and an outward potassium current (I_{Kur} and I_{Ks}). Phase 3: repolarization by closure of the L-type calcium channels, and outward potassium currents (I_{Ks} and I_{Kr}) corresponding to the end of the T-wave on the ECG. Phase 4: a slow depolarization occurs if the current reaches the threshold, which initiates the next depolarization.

On the ECG the QT interval is defined as the time in milliseconds (ms) from the onset of the Q-wave to the end of the T-wave.[8] Determining the end of the T-wave can be difficult, and is the source most of the error. The most ac-

curate and reproducible method is the "tangent method,"[9] although other methods are available for more complex T waves.[8] In the tangent method, the end of the T-wave is defined as the intersection of the tangent of the rapid downslope of the T-wave and the iso-electric T-P segment.[9] In general, the longest measured QT interval on a 12 lead ECG is used, as some leads may have isoelectric portions of the QT interval which may be erroneously left out of the QT measurement. Automated analysis programs use slightly different methods. For example, the common GE Marquette 12SL™ ECG Analysis Program measures the QT interval from the earliest detection of depolarization in any lead to the latest detection of repolarization in any lead.[10] However, these algorithms have proven to be highly reliable and reproducible, although their precision remains dependent on the overall ECG quality.[10]

THE CORRECTED QT (QT_c) INTERVAL

With increasing heart rates, the time between cardiac cycles shortens. As the duration of ventricular depolarization, measured as the QRS complex duration on the ECG, remains unchanged, ventricular repolarization has to shorten. Therefore, the uncorrected QT interval is highly dependent on heart rate. In order to compare QT intervals at different times and at different heart rates, the QT interval is corrected for heart rate with mathematical formulas and the QTc interval represents the QT interval at 60 beats per minute.[11] In 1920, Bazett[12] presented the first QT correction formula ($QTc=QT/RR^{1/2}$), which until today is still the most widely used formula in clinical practice. A major criticism of the Bazett formula is its overcorrection at higher and lower heart rates.[11,13,14] As the goal of QT interval correction is to remove its dependency of heart rate, studies that present QTc intervals corrected with Bazett formula and do not adjust for heart rate render inaccurate results that cannot be independently related to the QTc interval. In the same year, Fridericia already presented a more optimal method ($QTc=QT/RR^{1/3}$), that has more recently been shown to provide most accurate QT correction in patients with normal and abnormal heart rates when compared with other formulas.[14,15] Fridericia's formula also outperformed other formulas in atrial fibrillation and improved risk prediction for all-cause mortality.[14] A difficult population for QTc correction and interpretation are patients with ventricular conduction defects, defined as a QRS duration >120 ms. Over time, multiple adjustments or tricks have been suggested to correct the QT interval in these patients, however the Rautaharju formula [QT–0.155(RR–1)–0.93(QRS–0.139)+k with k=–0.022s for men and k=–0.034s for women] have been shown to correct for QRS duration, as well generating QTc values interpretable with common cutoffs for normal values and has been show to predict mortality as well.[14,16] In the acute setting at an emergency department, the use of appropriate QT correction formulas has shown to reduce the number of patients considered to have a prolonged QTc by 65%.[17] In patients with liver disease, the Fridericia formula has recently been shown to be superior over other formulas and its use is therefore recommended in patients with cirrhosis.[18-20]

Table 1. Normal Values for QTc Intervals by Sex[8]

QTc interval	Males	Females
Normal, ms	<430	<450
Borderline, ms	430–450	450–470
Prolonged, ms	>450	>470

QTc, corrected QT.

Identifying significant QTc prolongation starts with defining normal values (Table 1).[8] Overall, a QTc interval >450 ms in male and >470 ms in females are considered prolonged. More than a single QTc measurement, the change of the QTc interval in time is relevant, for example after starting a new potentially QT prolonging drug. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use has provided recommendations on the design, conduct, analysis, and interpretation of thorough QT/QTc studies, which intend to determine whether a drug has a threshold pharmacologic effect on cardiac repolarization. In these ICH E14 guidelines a significant QTc prolongation is defined as an increase in QTc >60 ms or an absolute QTc interval >500 ms.[21] The cutoff of >500 ms originates from observational studies in patients with congenital LQTS and a QTc >500 ms was associated with life-threatening cardiac events and TdP.[22-24]

LONG QT SYNDROME

The LQTS is a heterogeneous group of disorders which cause prolongation of cardiomyocyte repolarization. The LQTS in noncirrhotic populations can be divided in two forms, as described above. The congenital LQTS comprises patients with hereditary genetic mutations affecting cardiac ion channels.[25,26] Thus far, mutations in 16 different genes causing congenital LQTS have been identified. Despite this, 15% to 20% of congenital LQTS patients will not have a detectable gene mutation and may represent yet undiscovered LQTS genotypes or *de novo* mutations.[25] The acquired LQTS is predominantly caused by extrinsic factors which

influence cardiac repolarization. The pharmacological blockade of cardiac ion channels, either through on target (e.g., sotalol) or off target effects (e.g., cisapride) of a wide range of drug therapies, is by far the most common cause of acquired LQTS.[27] Most drugs that cause a LQTS do so through blockade of the delayed rectifier current potassium channel (I_{Kr}), which is coded by the human ether-a-go-go gene (hERG). Due to its promiscuous pore structure, a variety of drug moieties can bind to the hERG-channel and block its inner pore thereby reducing I_{Kr} currents resulting in slowing of phase 3 repolarization.[28] A complete list of drugs associated with a risk of QTc prolongation can be found at www.CredibleMeds.org.[29] They present 4 lists of drugs (1: drugs with a known risk for TdP, 2: drugs with a possible risk for TdP, 3: drugs with a conditional risk for TdP, and 4: drugs to be avoided by patients with congenital LQTS) that are being updated continuously based on available evidence. Further, inadvertent combination of these at-risk drugs may synergistically compound QT prolongation either through direct effects on cardiac ion channels or through induction or suppression of drug metabolism pathways (often cytochrome P450).

Also known to cause QT prolongation are bradycardia,[30] especially acutely following cardioversion of atrial fibrillation,[31] female sex,[32] electrolyte abnormalities such as hypokalemia and hypomagnesemia;[33] as well as structural heart disease such as hypertrophy,[34] ischemia,[35] and heart failure.[36,37] There may also be a potential contribution of genetic abnormalities in acquired LQTS after all. It is widely known that there is variable penetrance of the congenital LQTS with many phenotype negative, genotype positive patients.[38] An estimated 10% to 15% of silent congenital LQTS patients will be unmasked through consumption of a QT prolonging drug and may initially be considered as acquired LQTS.[39] In a recent study, about one-third of acquired LQTS patients actually carried a known congenital LQTS mutation and both common and rare genetic polymorphisms that could induce QTc prolongation when cumulated were described.[40]

In clinical practice the congenital and acquired LQTS represent opposite ends of a wide spectrum rather than 2 distinct disease entities. The overarching principle is that manifest LQTS is a multi-hit disease process. Typically, the combination of several risk factors is required to erode a patient's "repolarization reserve," to significantly prolong the QTc interval and establish a clinically relevant LQTS.[41] It is this complexity of LQTS, and its heterogeneity in presentation, that makes it hard to predict which patient will develop an acquired LQTS and should be considered at risk for TdP. Many risk scores to predict significant QTc prolongation have been developed, however only a few include liver disease.[37,42,43] The long-term association between a prolonged QTc and mortality has been studied extensively. In the Framingham Heart Study a prolonged QTc was associated with a 84% increased risk of all-cause mortality over a mean follow-up of 27 years, but there was no significant association specifically with sudden cardiac death.[44] In a large primary care population of 173 529 patients aged between 50 and 90 years with a mean follow-up of 6 years, a prolonged QTc was an independent predictor of all-cause mortality, cardiovascular mortality and non-cardiovascular mortality in both men (hazard ratio 2.53, 4.08, and 2.14, respectively) and women (hazard ratio 1.52, 2.09, and 1.38, respectively).[45] These findings were confirmed in an in-hospital population.[11,14] The short-term predictive value for a prolonged QTc at the emergency department to predict in-hospital mortality was limited, whereas a severely prolonged QTc >500 ms was associated with in-hospital cardiovascular events.[17]

TORSADE DE POINTES

The most severe complication of LQTS is the idiosyncratic polymorphic ventricular tachycardia TdP (Fig. 2).[6] TdP is often self-limiting and reverts back to sinus rhythm, but can also deteriorate into ventricular fibrillation and lead to sudden cardiac death. The term TdP was introduced by Dessertenne[46] in 1966 due to the typical pattern of twisting points. The electrocardiographic features of TdP are first, a twisting change in the morphology and amplitude of the ventricular activity around the isoelectric baseline.[6] However, since each ECG lead presents data from its corresponding vector through the heart, this may not be seen in all leads. Second, the initiation of TdP is typically

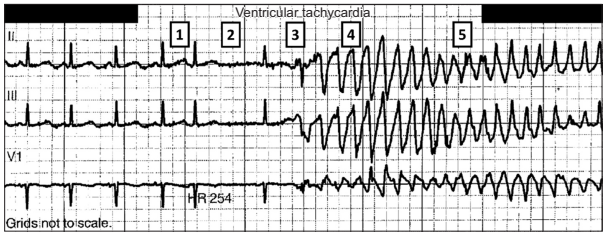

Fig. 2. Continuous electrocardiogram monitoring strip of a patient with torsade de pointes (TdP) ventricular tachycardia. Typical electrocardiographic presentation of TdP ventricular tachycardia. 1: Short-coupled premature atrial beat. 2: Compensatory pause after the premature atrial beat. 3: Short-coupled premature ventricular beat resulting in a "short-long-short" (1-2-3) sequence initiating TdP. 4: Warm-up phenomenon with slightly longer RR intervals initially. 5: Typical twisting morphology and amplitude of the ventricular activity around the isoelectric baseline during TdP.

preceded by a "short-long-short" sequence with a longer than usual pause and then a short-coupled premature ventricular beat on the next T-wave, which is the vulnerable phase of the myocardium. Third, TdP illustrates a warm-up phenomenon in the first beats of the arrhythmia with longer RR-intervals before the typical pattern of TdP starts. The self-limiting properties imply that the true incidence of TdP is unknown, but only estimated. In hospitalized patients the incidence of TdP in patients with acquired LQTS was estimated at 0.016% per year based on data collected over a 3-year period in a tertiary care hospital.[47]

The pathophysiology and arrhythmogenesis of TdP starts with a prolonged repolarization of the ventricular action potentials due to a decreased repolarizing potassium current, usually due to I_{Kr} blockade (Fig. 3).[48,49] On a cellular level, this may lead to "early afterdepolarizations," which occur when the membrane potential remains sufficiently high to re-open voltage-gated L-type calcium channels after they are no longer refractory. If this early afterdepolarization reaches the threshold to initiate a ventricular contraction, then this is called "triggered activity" which causes the short-coupled premature ventricular beat on the T-wave that can initiate TdP.

There are regional differences in ventricular action potential duration throughout the myocardium. Mid-myocardial M-cells show a proportional higher increase in action potential duration with I_{Kr} blockade compared to epicardial and endocardial cells. This results in a transmural dispersion of ventricular repolarization as cells with a slightly prolonged action potential are next to cells with a much longer action potential duration. In contrast to the normal pattern of depolarization and repolarization of the ventricular myocardium, this ventricular repolarization gradient means that depolarized cells are very close to cells that are no longer refractory, separated by a layer of cells with a very long refractory period. When this transmural dispersion reaches an arrhythmic threshold and coincides with triggered activity, this may result in an intra-mural reentrant circuit causing TdP.

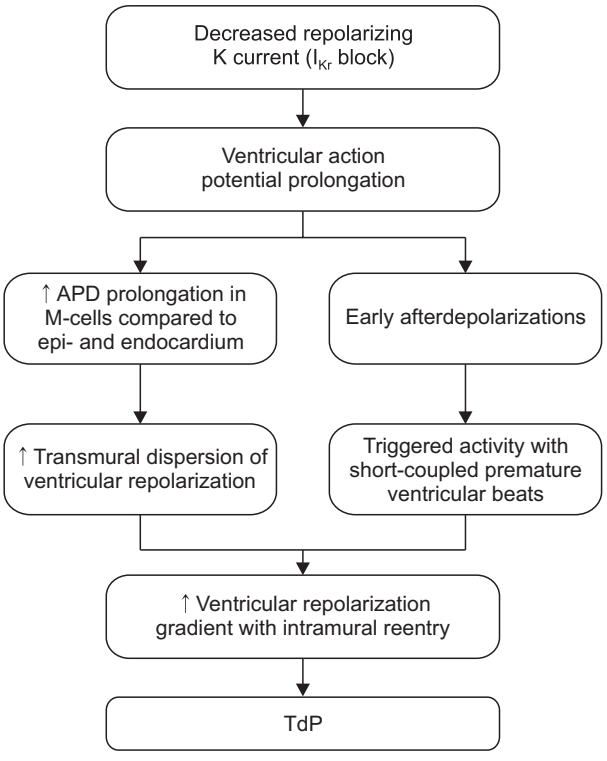

Fig. 3. Arrhythmogenesis in torsade de pointes (TdP) ventricular tachycardia. Flowchart presenting the arrhythmogenesis of TdP ventricular tachycardia.
APD, action potential duration; M-cells, mid-myocardial M-cells.

As can be deduced from the above, the likelihood of developing TdP depends on coincidences. As a result, the ability to predict who will develop TdP is fairly limited. On a population level, due to the many factors that influence the QTc interval (e.g., obesity, diabetes, cardiomyopathies, and neurological disorders), a prolonged QTc interval may reflect a generic, long-term risk factor, unless acute changes in the QTc interval are present which may serve as a short-term risk factor.[17] Several of these acute ECG features associated with development of TdP have been described, such as short-term QT variability,[50] T-wave alternans,[51] T-peak to T-end time,[52] and T-wave notching.[53] As most of these features are associated with imminent TdP, within minutes or hours, their utility for guidance of long-term therapy and risk reduction is limited.

ACQUIRED LQTS IN CIRRHOSIS

The wide range of QT prolongation in cirrhosis that is reported between 30% and 70% does not allow an exact estimate of the prevalence of acquired LQTS in these patients.[2,3] There are several factors underlying the significant discrepancies in the literature. First, the vast majority of studies are retrospective with the inherent limitations of this design. Second, cirrhosis or chronic liver disease has many etiologies and liver dysfunction runs the gamut from mild dysfunction to end-stage liver failure with an expected untransplanted survival measured in months. This implies significant heterogeneity in study populations due to selection bias. Third, most studies report QTc intervals with the Bazett formula and therefore present overestimated QTc values. Lastly, a prolonged QTc was not defined consistently, and endpoints differed between studies. It is therefore not surprising that there are widespread discrepancies in the literature. As a result, there is an under-ap-

preciation of the magnitude of the prevalence and severity of this disease in the cirrhosis population which can affect clinical decision-making since certain hepatic pathologies and/or treatments can further impact on cardiac repolarization.

In the setting of cirrhosis, the presence of LQTS can present as a clinical conundrum with a variety of non-hepatological issues to consider. This is supported by the observation that in patients with a prolonged QTc prior to liver transplantation, the QTc interval normalized in over half of the patients after transplant.[54-56] Hence, cirrhosis has an independent effect associated with QT prolongation, but these may at least be partially reversible. Besides known extrinsic causes, such as off-target I_{Kr} blockade of drugs, induction or suppression of cytochrome P450 drug metabolism pathways, and electrolyte abnormalities exacerbated by loop diuretics, the mechanisms underlying QT prolongation in cirrhosis are poorly understood. There are a variety of proposed mechanisms, but there remains a paucity of published literature which adequately examines these mechanisms in a comprehensive translational manner from bench to bedside.

One such proposed mechanism is the accumulation of hepatic metabolites such as bile acid salts.[57,58] There is evidence that cardiac myocytes express nuclear bile acid receptors: farnesoid-X receptor[59] and Takeda G-protein receptor 5.[60,61] The underlying cellular pathophysiology was studied by Ward *et al.*[62] in bile duct ligated-cirrhotic rats and they found a decrease in expression of I_{to} and I_{Kur} resulting in prolonged action potential duration. In contrast, patch clamp experiments of ventricular cardiomyocytes perfused with bile acids demonstrated a decrease in inward Ca^{2+} currents and an increase in outward K^+ currents, the net result being an overall shortening of the QTc.[63] However, the latter was performed in otherwise healthy rat myocardium, whereas the former study was performed after bile duct ligation. Moreover, multivariate analysis of serum bilirubin, serum cholic acid and serum ursodeoxycholic acid failed to show a significant correlation with QTc prolongation in human cirrhosis patients.[5] Further, studies have observed QT prolongation in patients with portal hypertension when compared to healthy controls and patients with normal portal pressures.[64] This QT prolongation was also observed in patients with noncirrhotic portal hypertension. Portosystemic shunting results in dumping cardiotoxic substances, bile salts, endotoxin and cytokines into the systemic circulation, which may have a detrimental effect on cardiomyocytes. The insertion of a transjugular intrahepatic portosystemic shunt was also associated with a sustained increase in QTc interval.[65]

Another possible mechanism is autonomic nervous system dysfunction which is a common phenomenon and is associated with a poor prognosis in cirrhosis patients.[66] Additionally, autonomic imbalance has been shown to affect QT prolongation.[67,68] Therefore, autonomic dysfunction in the setting of cirrhosis could potentially produce manifest LQTS. In support of this, Bernardi *et al.*[5] demonstrated a positive association between QT interval and plasma norepinephrine in cirrhosis patients which suggests an adverse response to increased sympathetic nervous system tone. Moreover, unpublished data from the same group showed use of beta-blockers decreased the QTc interval for the same cirrhosis population.[69] In contrast, two studies were unable to show an association between cardiac autonomic neuropathy and LQTS in the setting of cirrhosis.[70,71] The extent to which autonomic dysfunction contributes to LQTS in the setting of cirrhosis is not yet fully understood.

Classically, female sex but specifically estrogen, is known to be a risk factor for acquired LQTS. The QT interval of normal males and females diverge after puberty,[72] and in females the QT interval cycles in synchrony with the menstrual cycle, averaging 10 ms shorter in the luteal phase (low estrogen-high progesterone) compared to the follicular phase (high estrogen–low progesterone).[73] Moreover, studies have also demonstrated the QT shortening effects of testosterone and progesterone.[74,75] Similarly, hypoandrogenism and hyperestrogenism is observed in cirrhosis due to increased peripheral conversion of androgen sex hormones to estrogen.[76] Interestingly, in contrast to the normal population, there is no sex difference in QT prolongation in LQTS cirrhosis patients, suggesting that these secondary peripheral conversion mechanisms have suppressed the normal gonadal hormone influence on QT interval.[5,56,77]

The presence of cardiomyopathy and heart failure itself are well-known risk factors for acquired LQTS.[34,36,37,78] The levels of brain natriuretic peptide and pro-brain natriuretic peptide, cardiac peptides reflecting ventricular dysfunction, are increased in cirrhotic patients and correlate with the severity of disease and the QT interval.[79] Several conditions such as excessive alcohol consumption, hemochromatosis and cirrhotic cardiomyopathy may induce both cirrhotic and cardiomyopathic disease processes. Bernardi *et al.*[5] demonstrated that there was no difference in QT interval between alcoholic cirrhosis and non-alcoholic cirrhosis, suggesting that the cirrhosis itself is the driving factor in QT prolongation and not a common underlying pathophysiological mechanism which independently causes both cirrhosis and LQTS. The pathophysiology of cirrhotic cardiomyopathy itself is yet to be fully elucidated. Biochemical mechanisms such as lipopolysaccharide,[80] tumor necrosis factor-α,[81] endocannabinoids[82] and dysregulation

of β-adrenergic receptors[83] contribute to the pathogenesis of cirrhotic cardiomyopathy. However, what role these mechanisms play in the genesis of repolarization abnormalities in cirrhosis remains unclear. Indeed, a recent study by Koshy *et al.*[84] demonstrated no correlation between LQTS and either the 2005 World Congress of Gastroenterology or 2020 Cirrhotic Cardiomyopathy Consortium diagnostic criteria for cirrhotic cardiomyopathy,suggesting that LQTS and cirrhotic cardiomyopathy are separate and unrelated phenomena. However, this conclusion is controversial, with some believing that he presence of cirrhotic cardiomyopathy may contribute to the manifestation of LQTS, and also increase the risk of fatal arrhythmias.[85]

RISK OF LQTS IN CIRRHOSIS

Despite the lack of understanding about the underlying mechanisms of cirrhosis related acquired LQTS, the clinical significance of cardiac-hepatic interactions cannot be overstated. Specifically, the key question is whether acquired LQTS in cirrhosis is pro-arrhythmic, similar to the noncirrhotic patients with LQTS. If so, a failure to recognize these interactions could result in severe arrhythmic consequences for the patient.

The literature on the predictive value of a prolonged QTc interval in patients with cirrhosis is unclear due to heterogeneous study designs with different exclusion criteria, different levels of characterization of the study population, use of different correction formulas and lack of time-to-event analysis. Multiple studies reported on the association between the QTc interval and mortality in patients with cirrhosis. Kazankov *et al.*[20] and Zhao *et al.*[86] reported no predictive value for a prolonged QTc interval in their prediction models, whereas Kim *et al.*[87] reported a 69% higher mortality rate in patients with a prolonged QTc interval. Further, Biselli *et al.*[88] reported an increased short-term mortality within 6 weeks after admission of patients with cirrhosis for gastrointestinal bleeding, on top of the Model for End-Stage Liver Disease-sodium (MELD-Na) score. In multiple studies, the QTc interval was significantly associated with measures of disease severity, such as liver function tests and the Child-Pugh score.[5,19,54,86]

Data after liver transplantation are again conflicting. Ko *et al.*[89] reported changes in QTc intervals after transplant and reported QTc shortening in 73% of patients. They did not observe an association between the QTc interval after transplantation and mortality during follow-up. Similar results were presented before in smaller populations.[19,54] Lee *et al.*[90] reported no significant difference in outcome when using an ECG prior to the transplant, but a 78% higher mortality if QTc prolongation was present 1 month after liver transplant.

MANAGEMENT OF LQTS IN CIRRHOSIS

Based on the available literature, it is safe to state that there is a significant association between the QTc interval and the severity of liver disease. There may also be a significant association with mortality. When treating cirrhosis patients there are specific clinical scenarios which may worsen QT prolongation and therefore increase the risk of TdP. Acute awareness of these situations may help to avoid calamity, but at a cost of limiting treatment options for a patient. Table 2 presents relevant risk factors which should be assessed and (and prevented when possible) in case of acquired LQTS.

First, each cirrhosis patient should have a good quality 12-lead ECG available to assess a baseline QTc interval. The presence of a prolonged QTc interval at baseline, as a measure of reduced repolarization reserve, may be a strong predictor to develop acquired LQTS in the future.[91] This could be combined with a thorough cardiovascular examination, including familial history and history of previous arrhythmias.[37] If a patient presents with significant QTc

Table 2. Risk Factors to Assess in the Presence/Prevention of Acquired Long QT Syndrome

Risk factor	Mitigation strategy
Previous QTc prolongation	Check prior ECGs to establish a baseline QTc interval
Prior cardiovascular history	Thorough assessment of cardiovascular history
Acute illness and infection	Physical examination and treat infections
Known QT prolonging drugs	Check lists 1 and 2 on CredibleMeds.org
Conditional QT prolonging drugs	Check list 3 on CredibleMeds.org
Electrolyte abnormalities	Check and correct potassium, magnesium and calcium levels
Thyroid disturbances	Check thyroid function and replacement therapies
Bradycardia-arrhythmias	Assess for pacing indication and anti-arrhythmic therapy
Cardiomyopathy	Diagnose and treat according to most recent guidelines

QTc, corrected QT; ECG, electrocardiogram.

prolongation, this patient should be assessed for acute illnesses and infections, as these may further impact the outcome.[92] Patients presenting with sepsis, bleeding or liver failure, should be closely monitored for electrophysiological abnormalities, including continuous cardiac monitoring.[92] Additional investigations may be needed, including biochemistry with electrolytes, and thyroid indices.[92,93]

Although many clinicians caring for severely ill cirrhotic patients have almost never observed TdP in this population and thus believe that it may be a rare arrhythmia even in those with prolonged QTc, this might be an inaccurate opinion. The majority of cirrhotic patients dying of end stage liver failure, or acute-on-chronic liver failure precipitated by conditions such as sepsis, bleeding, or other insults, usually do not undergo continuous ECG monitoring. It is therefore quite possible that the agonal event in many such patients is a significant arrhythmia, and a death ascribed to "liver failure" may actually have been a sudden cardiac death.

By far the most common cause of acquired LQTS is a drug-drug interaction.[27] Some classes of medication with well-known I_{Kr} affinity are frequently used in cirrhosis patients, including fluoroquinolone antibiotics, antidepressants, anti-emetics and analgesics. These can be found at www.CredibleMeds.org in lists 1 and 2.[29] As described above, drug-drug interactions are not necessarily restricted to off-target I_{Kr} blockade, but could also result from suppressed cytochrome P450 enzyme activity due to hepatic impairment. Carbamazepine, for example, has modest hERG affinity in the micromolar range,[94] but severe QT prolongation can occur when combined with a macrolide antibiotic such as erythromycin, due to CYP3A4 inhibition leading to significant increase in bioavailability of carbamazepine.[95] Activity of CYP1A, 2C19 and 3A are more sensitive to cirrhosis, whereas 2D6, 2C9 and 2E1 seem less affected.[96] When no drugs from www.CredibleMeds.org lists 1 or 2 can be identified, one can often identify drugs that exacerbate other LQTS risk factor (www.CredibleMeds.org list 3).[29] Examples include loop diuretics and proton pump inhibitors. Loop diuretics are often used in the treatment of ascites, but if unmonitored these can lead to massive urinary losses of potassium and magnesium and resultant hypokalemia and hypomagnesemia.[37,97] The use of proton pump inhibitors is associated with hypomagnesemia and have shown to be related to the risk of TdP.[98] A practical approach to mitigating risk associated with drug-induced LQTS to is refer to the aforementioned lists of QT prolonging drugs whenever commencing a new drug therapy on a LQTS patient. In many cases, non-QT prolonging alternatives are available, without losing too much efficacy, for example antidepressants. Importantly, many of the QT prolonging effects are idiosyncratic to the specific molecules, and not due to a "class effect."

Bradycardia, either due to sick sinus syndrome, atrioventricular block or cirrhosis-related chronotropic incompetence, can result in an excessive increase of QT prolongation,[99] and put the patient at risk of the "short-long-short" sequences which typically initiate TdP. In severe cases, a cardiac pacing strategy programmed with a sufficiently fast lower rate may be recommended.[100] In many cases, the cardiac substrate for arrhythmia may be more complex. Heart failure in itself is a risk factor for TdP[36] as well as other ventricular arrhythmias.[101] Cirrhotic cardiomyopathy can be both a risk factor for cirrhotic LQTS, as well as an exacerbating factor cirrhotic LQTS.[3] Therefore, a thorough cardiac evaluation, including a plasma brain natriuretic peptide level and a transthoracic echocardiogram, is indicated in case of high clinical suspicion, as these cardiac conditions would require dedicated heart failure and arrhythmia management. Beta-blockers are protective against arrhythmias in the LQTS-cirrhosis population most likely due to their sympathomimetic effect.[5,102]

In patients with cirrhosis, multiple hits and cardiac-hepatic interactions are often required to sufficiently erode the repolarization reserve before manifest acquired LQTS and TdP can occur. Physicians should have a high index of clinical suspicion for acquired LQTS when treating cirrhosis patients. Whilst some risk factors (e.g., medical conditions, cardiovascular conditions and genetic predisposition) are unavoidable, the patients' risk of developing acquired LQTS can be mitigated by avoiding drug interactions, electrolyte imbalances and ECG monitoring. In some cases, a joint effort by cardiologists and hepatologists may be needed, and this may significantly improve a patient's clinical course and outcome.[87]

CONCLUSION

Cirrhosis-related LQTS is common and can significantly affect a patient's therapeutic options as well as long-term prognosis. Some efforts have already been undertaken to understand the etiology of this disease, but the true mechanistic pathophysiology remains elusive. Areas of interest may include metabolic, autonomic or hormonal imbalances, cirrhotic heart failure and/or genetic predisposition.

In practice, a high index of clinical suspicion is required to avoid drug interactions and to mitigate other risk factors in an effort to reduce the risk of QT prolongation and fatal arrhythmias. When severely ill cirrhotic patients, whether pre- or post-transplant, are admitted for complications such as sepsis, bleeding or liver failure, we recommend that

they be closely monitored for electrophysiological abnormalities. In those with a prolonged QTc continuous ECG monitoring should be strongly considered.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

B.V. is supported by a research grant of the Frans Van de Werf Fund for Clinical Cardiovascular Research (Leuven, Belgium). S.R.R. receives research support from the Canadian Institutes of Health Research (grant MOP142426). This work was supported in part by the National Center for Advancing Translational Sciences (NCATS) Award UL1 TR000445.

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