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Relationship between QT-interval prolongation and structural abnormalities in cirrhotic cardiomyopathy: A change in the current paradigm

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Abbreviations

QTc: Corrected QT-interval
2005-WCG: World College of Gastroenterology 2005
2020-CCC: Cirrhotic Cardiomyopathy Consortium 2020

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DSE: dobutamine stress echocardiography
TTE: transthoracic echocardiography
ECG: electrocardiogram
MELD: model for end-stage liver disease
bpm: beats per minute
ms: milliseconds

Abstract

It is postulated that cardiac structural abnormalities observed in cirrhotic cardiomyopathy (CCM) contribute to the electrophysiologic abnormality of QT-interval (QTc) prolongation. We sought to evaluate whether QTc prolongation is associated with intrinsic abnormalities in cardiac structure and function that characterize CCM. Consecutive patients undergoing liver transplant work-up between 2010-2018 were included. Measures of cardiac function on stress testing including cardiac reserve and chronotropic incompetence were collected prospectively and a corrected QTc≥440ms was considered prolonged. Overall, 439 patients were included and 65.1% had a prolonged QTc. There were no differences in markers of left ventricular and atrial remodelling, or resting systolic and diastolic function across QTc groups. The proportion of patients that met the criteria for a low cardiac reserve (39.2 vs 36.6%, p=0.66) or chronotropic incompetence (18.1 vs 21.3%, p=0.52) was not different in those with a QTc≥440 vs <440 ms. Further, there was no association between QTc-prolongation and CCM by either the 2005 World College of Gastroenterology or modified 2020 Cirrhotic Cardiomyopathy Consortium criteria. *Conclusion:* QT-interval prolongation was not associated with structural or functional cardiac abnormalities that characterize CCM. These findings suggest that CCM and QT-interval prolongation in cirrhosis may be two separate entities with distinct pathophysiological origins.

Introduction

Liver dysfunction and portosystemic shunting of vasodilators and cardio-suppressive factors are thought to lead to cirrhotic cardiomyopathy (CCM) - a disorder characterized by abnormalities in cardiac structure and function.(1-4) CCM fundamentally refers to systolic dysfunction, altered diastolic indices and an impaired contractile response to stress in patients with end-stage liver disease and no known

cardiac disease.(1, 5, 6) Historically, QT-interval prolongation has been regarded as the electrophysiological hallmark of CCM and is present in 30-60% of patients undergoing liver transplantation.(1, 7-11) The structural and electrophysiological features of CCM were collectively regarded as one entity according to the 2005 World Congress of Gastroenterology (2005-WCG) definition, which lists QT-interval prolongation as a supporting criterion for the diagnosis of CCM.(5) This was subsequently rescinded by the 2020 Cirrhotic Cardiomyopathy Consortium (2020-CCC) criteria, which highlighted QT-interval prolongation as an important area for future research.(1) While studies have postulated that structural and histological changes in cardiac chambers including subendocardial edema, patchy fibrosis, potassium channel abnormalities and sympathoadrenergic hyperactivity contribute to the QT-interval prolongation observed in cirrhosis, none have verified this hypothesis.(9, 12-15) Therefore, we sought to examine whether QTc prolongation was associated with resting and stress-induced cardiac structural abnormalities that characterize CCM.

Methods

Consecutive adult (age ≥18 years) patients that underwent cardiac assessment prior to undergoing liver transplantation between 2010 and 2018 at the Victorian Liver Transplantation Unit, Melbourne, Australia were assessed for inclusion in this retrospective cohort study. Only patients with a 12-lead electrocardiogram (ECG) and cardiac structural assessment with pre-transplant dobutamine stress echocardiography (DSE) or transthoracic echocardiography (TTE) prior to liver transplantation were included. Patients were excluded if they were undergoing re-transplantation, had significant unrevascularized coronary artery disease, valvular heart disease, cardiomyopathy, or if patients were transplanted for hemochromatosis/amyloidosis. The project received approval from the Human Research Ethics Committee at Austin Health.

Patient demographics, medical history, etiology, and severity of liver disease (based on the model for end-stage liver disease [MELD] score and Child-Pugh score) were obtained from the prospectively collected institutional liver transplant database and supplemented by individual case review of the medical records as required. Diagnosis of cirrhosis was made on histology and/or on clinical, laboratory, and

ultrasonography findings. Blood samples were taken for the measurement of liver function, urea, serum electrolytes, and creatinine before the echocardiography.

Echocardiographic data were collected prospectively and subsequently extracted for the purpose of this study. The decision for referral for a DSE or a TTE was performed as per the institutional protocol.(16) All patients had resting echocardiographic assessment, which included tissue Doppler indices. Echocardiographic images including valvular assessment were obtained according to American Society of Echocardiography guidelines.(17) The protocol for DSE at our institution has been published previously.(16) Briefly, dobutamine was administered intravenously and incrementally increased at 3-minute intervals from the starting rate of 5 mg/kg/min to a high dose (20–40 mg/kg/min) to achieve ≥85%of the maximum predicted heart rate for age. Cardiac output (CO) was calculated as the product of left ventricular stroke volume x heart rate (beats per minute), derived from concurrent ECG tracing. A low cardiac reserve was defined as ΔCO <25% on low-dose dobutamine (10μg/kg/min), based on previous validation by our group.(16) Chronotropic incompetence was defined as those attaining less than 85% of the age-predicted maximum heart rate (calculated as 220 beats per minute - age) at peak-dose dobutamine (40 mg/kg/min).(18) β-blockers were ceased in all patients 72 hours prior to DSE.

All ECGs were reviewed independently by a cardiologist blinded to clinical details. The QT interval was assessed manually using the average of three consecutive QT intervals in leads free of noise and ectopic beats. The QT interval was corrected (QTc) according to the Bazett formula (QTc=QT inteval/$\sqrt{}$RR interval).(19) A QTc≥440 millisecond (ms) was considered prolonged. A detailed description of the methodology and reproducibility of QTc measurement from our group has been published previously.(7)

The primary aim was to determine the association between QTc prolongation and structural cardiac abnormalities on resting and stress echocardiography. The secondary aim was to evaluate the co-existence of QTc prolongation and CCM using the 2005-WCG or the 2020-CCC consensus definitions.(1) This study included

modified 2020-CCC criteria: resting echocardiographic indices and impaired cardiac reserve without left ventricular strain assessment.(1)

Statistical Analysis

Results are expressed as mean ± standard deviation or median with interquartile range (IQR) for non-normally distributed data. Comparisons between groups were performed with the chi-square test for categorical data. Continuous parametric data was assessed using the Student t-test while continuous non-parametric data was assessed using the Mann-Whitney U test. All reported p values are two-tailed, with $p< 0.05$ considered significant. Statistical analysis was performed using Stata 13/MP (Statacorp, College Station, TX, USA).

Results

In total, 439 patients (mean age 56.9 ±12 years, 32.3% female) were included in the study analysis. Hepatitis B/C was the leading etiology of liver cirrhosis. A prolonged QTc ≥440 ms was observed in 271 (61.7%) patients. Baseline characteristics and cardiovascular risk factors were comparable when stratified by a prolonged QTc (Table 1).

Comparison of structural changes, including markers of left ventricular and atrial remodelling, demonstrated comparable values across both QTc groups. Similarly, markers of diastolic and systolic function, including tissue Doppler indices and ejection fraction were not significantly different between the groups (Table 1).

Evaluation of cardiac output indices, assessment of cardiac reserve and chronotropic incompetence was undertaken in patients undergoing DSE (n=325, 74.0%). Neither resting CO (7.3 ±2.0 L/min vs 6.9 ±2.3 L/min, p=0.16) nor the proportion of patients who met the criteria for a low cardiac reserve (39.2% vs 36.6%, p=0.66) or chronotropic incompetence (18.1% vs 21.3%, p=0.52) was different in those with prolonged QTc and those without, respectively.

A substantially higher proportion of patients met the 2005-WCG definition as opposed to the 2020-CCC definition of CCM (48.9% vs 3.7%, respectively). This difference was primarily driven by the inclusion of a blunted cardiac contractile

reserve on stress testing in the WCG-2005 criteria. Overall, there was no association between QTc-prolongation and the presence of CCM using either the 2005-WCG or 2020-CCC criteria (Figure 1). As the 2020-CCC diagnostic criteria include a low cardiac reserve and chronotropic incompetence as supportive criteria for establishing a diagnosis of CCM, additional sensitivity analyses were performed using these parameters. The inclusion of these indices did not significantly affect the relationship between QTc and CCM (Figure 1). Furthermore, neither a QTc cut-off point of 480ms nor the Fridericia's formula for correction of QTc affected the relationship between QTc and CCM criteria (data not shown).

Discussion

QT-interval prolongation is present in over 50% of patients with end-stage liver disease.(1, 7, 11) The preponderance of this electrophysiological abnormality in patients with cirrhosis coupled with its inclusion in the 2005-WCG criteria led to QT-interval prolongation being considered synonymous with a diagnosis of CCM.(5) However, several crucial differences exist between the cardiac structural and electrophysiological abnormalities in cirrhosis. Structural abnormalities including left ventricular remodelling, diastolic function and a low-cardiac reserve have been implicated in the pathogenesis of conditions including hepatorenal syndrome (HRS), cardiac decompensation and mortality.(12, 16, 20, 21) QT-interval prolongation on the other hand, increases the risk of post-transplant cardiac arrest with insufficient evidence linking it to cardiac decompensation, HRS or poor survival.(3, 7, 9, 22-24) Moreover, unlike cardiac structural changes, there are concordant lines of evidence indicating a reversal of QT-interval prolongation following liver transplantation.(1, 9, 11, 20, 25) These observations call into question the relationship between QT-interval prolongation and the more established markers of cardiac structural and autonomic abnormalities in cirrhosis, including systolic and diastolic function, cardiac contractile reserve and chronotropic incompetence.(1, 21)

The current study, which evaluated a large cohort of patients with end-stage liver disease demonstrated no significant differences in resting or stress induced cardiac indices when stratified by the presence or absence of QTc prolongation at baseline. Moreover, patients with a prolonged QTc were no more likely to fulfill either the original or the contemporary CCM diagnostic criteria.(1) This observation supports

the assertion of the 2020-CCC consensus document that QTc prolongation may have limited value in confirming a diagnosis of CCM.(1) Importantly, this also indicates that the structural cardiac abnormalities that characterize CCM may be intrinsically different to the pathophysiology that drives QT-interval prolongation in cirrhosis. Future studies are needed to distinguish between triggers driving both myocardial and electrophysiological changes in patients with liver cirrhosis. Whether LT itself leads to a reversal of CCM is also unclear.(20) Efforts to investigate whether resting and stress induced cardiac indices normalize following LT are essential.

From a clinical perspective of a transplant physician or cardiologist, grading the severity of CCM in patients undergoing LT is of importance. Despite prior reports indicating that QT-interval prolongation may be a consideration in this regard, our findings highlight a disconnect between the structural and electrophysiological characteristics.(5) While the 2020-CCM guidelines have proposed new criteria for the diagnosis of cirrhotic cardiomyopathy, there is insufficient data at present to grade the severity based on the criteria or whether severe CCM can preclude transplantation.(1) Risk stratifying patients that develop fulminant cardiac failure intraoperatively or with afterload reduction following reversal of systemic vasodilation, should be a key focus when establishing clinical severity criteria in a LT cohort. Previous work on this front has indicated a number of clinical variables including diastolic indices, BNP and stress testing findings.(26-28) Future studies validating the 2020-CCM guidelines as well as the use of novel indices are imperative to address this question and further refine our risk stratification within this patient cohort.

Strengths of this study include the large cohort, prospectively collected echocardiographic data and a rigorous methodology for QTc measurements. Additionally, this study includes analysis of inotropic and chronotropic reserve on stress testing which is pertinent as cardiac dysfunction in CCM can be unmasked by haemodynamic stress.(29) However, several limitations warrant mention. First, this study evaluated only patients with end-stage liver disease undergoing transplant evaluation. Whether these findings are generalizable to a non-transplant cohort with cirrhosis is unclear. Second, as all echocardiographic data were prospectively collected and pre-dated the 2020-CCC definition, we were unable to include left

ventricular global longitudinal strain measurements, an early marker of systolic impairment. This raises the possibility of misclassification bias and is important to address in future studies, as myocardial deformation indices may be a more sensitive marker of subclinical cardiac dysfunction in patients with a cirrhosis who typically exhibit a hyperdynamic resting cardiac output. Third, the use of the Bazett's formula may result in QTc overcorrection in cirrhosis.(8) However, the Bazett's correction for the QT-interval, which has been validated previously by our group(7) remains the most widely used in clinical practice and the findings were not altered when correction of the QT interval was made using the Fridericia's formula. Lastly, the observational, retrospective study design may be subject to implicit bias. This includes exclusion of patients with pre-existing cardiomyopathy and valvular heart disease and the use of DSE imaging in only a proportion of the study population. Given the retrospective design, there is also potential for bias, although this was minimized by independent review of ECGs as well and echocardiographic data by independent cardiologists in a blinded fashion.

Conclusion

QT-interval prolongation was not associated with structural or functional cardiac abnormalities that characterize CCM. These observations suggest that CCM and QT-interval prolongation in cirrhosis may be two separate entities with distinct pathophysiological origins.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*

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Data Availability Statement

The data are not publicly available due to the institutional ethical restrictions

Figure Legend

Figure 1: Comparison of Patients meeting the Cirrhotic Cardiomyopathy Criteria stratified by the corrected QT-interval (QTc)

2020-CCC, 2020 Cirrhotic Cardiomyopathy Consortium; 2005-WCG, World Congress of Gastroenterology (2005-WCG); QTc, corrected QT interval

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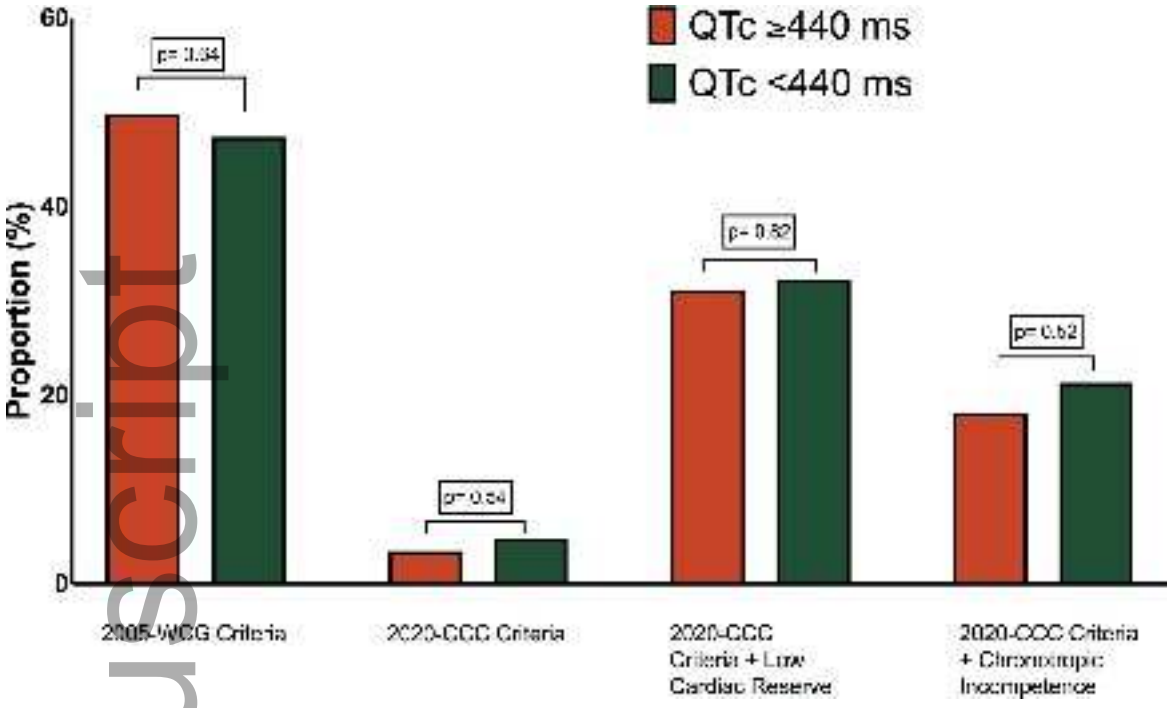
Table 1: Baseline Characteristics

	Overall (n=439)	QTc ≥440 msec (n=271)	QTc <440 msec (n=168)	p value
Age	56.9 ±12	57.6 ±12	56.3 ±12	0.28
% Female	32.3%	34.6%	27.8%	0.17
MELD score	17 ±6	19 ±7	17 ±5	0.68
Child-Pugh Score	9.5 ±3	9.8 ±2	9.2 ±3	0.08
Encephalopathy (≥Grade 1)	43.0%	44.4%	40.5%	0.48
Refractory ascites	T4.7%	48.2%	37.1%	0.09
Hepatorenal syndrome	19.9%	20.2%	18.8%	0.68
Etiology of Liver Disease				0.77
Hepatitis B/C	32.7%	70.0%	30.0%	
NASH	12.4%	64.0%	36.0%	
Alcoholic	9.5%	67.6%	32.4%	
HCC	8.9%	69.4%	30.6%	
Other	36.4%	62.9%	37.1%	
Deceased	49 (11.2%)	36 (13.3%)	13 (7.8%)	0.2
Cardiovascular risk factors				
Hypertension	40.6%	38.6%	44.4%	0.27
Coronary artery disease	9.8%	10.8%	7.5%	0.31
Diabetes	31.2%	32.2%	29.3%	0.56
Smoking history	61.4%	60.5%	63.2%	0.60
Dyslipidemia	24.8%	21.8%	30.8%	0.07
Non-selective beta blocker use	20.9%	21.2%	20.3%	0.85
QT prolonging medication use	44 (10.2%)	33 (12.2%)	16 (11.8%)	0.98
Echocardiographic Indices				
Left atrial area (cm^2)	23.8 ±5.9	23.3 ±5.6	24.6 ±6.6	0.13
Right atrial area (cm^2)	18.5 ±4.7	18.1 ±4.8	19.3 ±4.5	0.10
Peak TR velocity (m/s)	2.6 ±0.5	2.6 ±0.5	2.5 ±0.4	0.90
PASP (mmHg)	26 ±8	26 ±8	26 ±7	0.81
PVR (Wood units)	1.56 ±0.4	1.59 ±0.4	1.50 ±0.3	0.12
LV end-diastolic dimension (cm)	4.9 ±0.6	4.9 ±0.5	5.0 ±0.7	0.13
LV end-systolic dimension (cm)	3.0 ±0.6	2.9 ±0.5	3.1 ±0.7	0.11
Interventricular septum (cm)	0.98 ±0.2	0.95 ±0.2	1.0 ±0.19	0.07
Posterior wall (cm)	0.93 ±0.2	0.92 ±0.2	0.96 ±0.2	0.13
Peak E velocity	0.93 ±0.3	0.95 ±0.3	0.89 ±0.2	0.15
Peak A velocity	0.77 ±0.2	0.78 ±0.2	0.75 ±0.2	0.61

A duration (ms)	131 ±23	133 ±24.5	128 ±20.3	0.22
E/A ratio	1.3 ±0.8	1.3 ±0.5	1.3 ±1.1	0.72
Deceleration time (ms)	200 ±50.4	198 ±45.6	205 ±58.7	0.40
E' septal	9.0 ±2.6	9.1 ±2.8	8.9 ±2.0	0.74
E' lateral	11.6 ±4.6	11.6 ±4.7	11.6 ± 4.3	0.99
E/e'	9.5 ±4.8	9.7 ±5.0	9.2 ±4.4	0.48
RVS'	15.4 ±3.9	15.0 ±3.7	16.2 ±4.4	0.16
Ejection fraction (%)	66.2 ±12	67.4 ±11	63.1 ±14	0.24
Baseline cardiac output (L/min)	7.2 ±2.1	7.3 ±2.0	6.9 ±2.3	0.16
Baseline stroke volume (ml)	105 ±31	107 ±30	101 ±33	0.16
Baseline HR (beats/min)	75 ±12	76 ±13	72 ±12	0.01
MAP (mmHg)	80 ±14	79 ±13	82 ±15	0.10
SVR (dynes/cm^{-5})	943 (727-1180)	924 (727-1097)	1053 (752-1333)	0.07
Low dose dobutamine CO (L/min)	10.0 ±3.1	10.2 ±3.1	9.6 ±3.1	0.15
Low dose dobutamine SV (ml)	106 (88-128)	108 (89-128)	99 (84-130)	0.23
Low dose dobutamine HR (bpm)	92 ±20	92 ±20	92 ±20	0.88
% Change CO from baseline	34.1 (16-54)	33.1 (12-51)	35.3 (16-61)	0.32
Peak dose dobutamine HR (bpm)	151 ±14	151 ±14	151 ±14	0.86
Low cardiac reserve (△CO ≤25%)	41.6%	41.9%	40.9%	0.86
Chronotropic incompetence (Peak HR <85%)	19.1%	18.1%	21.3%	0.52

Values presented as mean ±standard deviation, median (interquartile range), n(%)

MELD; model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation; CO; cardiac output; SV, stroke volume; MAP, mean arterial blood pressure; SVR, systemic vascular resistance



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