

## Original Article

# Corrected QT Interval and QT Dispersion in Cirrhotic Patients before and After Liver Transplantation

Mahmood Zamirian MD<sup>1</sup>, Maryam Tavassoli MD<sup>1</sup>, Kamran Aghasadeghi MD<sup>•1</sup>

## Abstract

**Background:** Liver cirrhosis is associated with different types of electrophysiological changes, including QT prolongation, which may adversely affect long-term prognosis of these patients. The aim of this study is to evaluate the effect of orthotopic liver transplantation (LT) on corrected QT (QTc) interval and QT dispersion (QTd) in cirrhotic patients of various etiologies.

**Methods:** We enrolled 249 patients with end-stage liver disease between 2004 and 2009 at Shiraz Transplant Research Center, Shiraz, Iran. The QTc interval and QTd were measured by 12 lead ECGs for baseline and at 3 months after LT. Mean QTc interval and mean QTd were calculated. A QTc interval above 440 ms was considered abnormal.

**Results:** Within 3 months following surgery, 6 patients died. There were 105 patients (43.2%) with prolonged QTc before transplantation; in 91 (86.6%) patients, the mean QTc normalized after transplantation (baseline:  $490.9 \pm 45.74$  ms; post-transplantation:  $385 \pm 48.74$  ms;  $P < 0.0001$ ). Fourteen patients (13.3%) had evidence of some shortening of the QTc interval although the QTc remained above the upper limit of normal. Prolongation of the QTc interval in cirrhotic patients was independent of the etiology of cirrhosis. A normal QTc was seen in 138 patients (56.7%) before transplantation, of which 4 (2.9%) developed prolonged QTc after transplantation.

The mean QTd decreased significantly after transplantation (baseline:  $30 \pm 20$  ms; post-transplantation:  $30 \pm 10$  ms;  $P < 0.0001$ ).

**Conclusion:** Many cirrhotic patients have prolonged QTc intervals before LT regardless of disease etiology. In the majority of patients this value returns to normal after LT, suggesting that liver cirrhosis has independent unfavorable, but reversible electrophysiological effects.

**Keywords:** Liver cirrhosis, liver transplant, QTc, QTd

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## Introduction

The QT interval is a measure of ventricular electrical recovery after excitation.<sup>1</sup> Acquired QTc prolongation has been described in association with cardiac diseases, electrolyte abnormalities (such as hypocalcemia, hypomagnesemia, and hypokalemia), and many commonly used drugs.<sup>2-3</sup> Prolonged QTc may provide the substrate for ventricular arrhythmias.<sup>2-7</sup>

Liver cirrhosis is associated with different cardiovascular abnormalities, including cirrhotic cardiomyopathy which is defined as a constellation of one or more of the following changes: 1) normal or augmented systolic function at rest but blunted contractile responsiveness to stress, 2) altered diastolic relaxation,<sup>8</sup> 3) structural abnormalities in the cardiac chambers,<sup>9-10</sup> and 4) electrophysiological changes such as prolonged QT.<sup>5</sup>

QT dispersion (QTd) has been defined as the interlead QTc variability (difference between maximum and minimum QT intervals). Increased QTd is a direct reflection of disparities in myocardial recovery.<sup>11-14</sup> Thus determination of QTd, as a noninvasive and inexpensive technique, may help to predict arrhythmic events in cirrhotic patients.

The aim of the present study is to evaluate the effect of orthotopic

liver transplant (LT) on QTc and QTd in cirrhotic patients of various etiologies.

## Materials and Methods

In this prospective cross-sectional study we enrolled 249 patients with confirmed cirrhosis between May 2004 and September 2009 at Shiraz Transplant Research Center, Shiraz, Iran. Patients were excluded if they had a history of cardiac disease (clinical or echocardiographic evidence of valvular heart disease, ischemic heart disease) or a family history of sudden cardiac death. We also excluded patients with electrolyte abnormalities such as hypocalcemia, hypomagnesemia, and hypokalemia. The causes of liver disease in these patients were as follows: 63 hepatitis B (HBV), 56 autoimmune hepatitis (AIH), 34 cryptogenic cirrhosis, 34 primary sclerosing cholangitis (PSC), 13 hepatitis C (HCV), 14 Wilson disease, 12 alcohol cirrhosis, and 17 other diagnoses (Table 1).

Out of the 249 patients, 6 transplant recipients died within 3 months post-LT and were not included for analysis. For the remaining 243 patients, two 12-lead ECG recordings were obtained, one before LT and another at 3 months post-LT. After computer scanning, QTc was measured by using measurement software with an accuracy of 2 ms. The end of the T-wave was defined as the intersection of the isoelectric line with the tangent to the point of inflection with the descending part of the T-wave.<sup>11,13</sup> If the T-wave endpoint was slurred or the U-wave was prominent, the lead was excluded. Leads in which the T waves were isoelectric or too low in amplitude were also excluded. Measured QT intervals were corrected for heart rate (QTC) with Bazett's formula.<sup>13,15</sup>  $QTC > 440$

**Authors' affiliations** <sup>1</sup>Department of Cardiology, Cardiovascular Research Center, Nemazee Hospital, Shiraz University of Medical Science, Shiraz, Iran.

**Corresponding author and reprints:** Kamran Aghasadeghi MD, Department of Cardiology, Cardiovascular Research Center, Nemazee Hospital, Shiraz University of Medical Science, Shiraz, Iran. Tel.: +98-917-313-8870;

Fax: +98-711-612-5601,

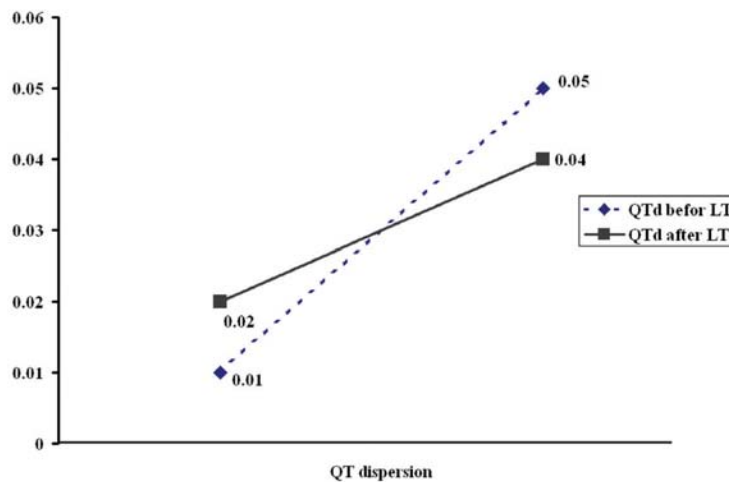
E-mail: aghasadk@sums.ac.ir

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**Table 1.** Relation between etiologies of cirrhosis and mean QTc before and after liver transplantation in 243 patients.

Cause of cirrhosis	Number of cases (%)	Mean QTc before liver transplantation*	Mean QTc after liver transplantation*
HBV	63 (25.9%)	483 ± 20	376 ± 53.06
AIH	56 (23.04%)	503 ± 32	390 ± 38
Cryptogenic	34 (14%)	510 ± 12	388 ± 53
PSC	34 (14%)	501 ± 38	384 ± 65.16
Wilson	14 (5.76%)	493 ± 18	393 ± 26
HCV	13 (5.35%)	482 ± 19	378 ± 16
Alcohol	12 (4.94%)	478 ± 25	365 ± 49
Others	17 (7%)	495 ± 23	381 ± 46.38

\* $P > 0.05$

**Figure 1.** Changes in QT dispersion before and after liver transplantation (LT).

ms was considered prolonged.

For calculating QTd, we identified the difference between the longest (QT maximum) and shortest (QT minimum) QT intervals in all 12 leads.

#### Statistical analysis

Statistical analyses were done with SPSS software (version 15). Pre- and post-transplant QTc data were analyzed with paired *t*-tests. Pre- and post-transplant QTd data were compared with McNemar's test. All results are expressed as the mean ± SD. *P* values less than 0.05 were considered statistically significant. Associations between QTc values and different etiologies of cirrhosis were compared with the Kruskal-Wallis test.

## Results

Of the 249 liver transplant recipients initially included (62% males, 38% females), 6 died within 3 months of surgery. The remaining 243 patients had mean QTc of  $446.9 \pm 12.53$  ms before LT that changed to  $382.92 \pm 48.79$  ms post-transplantation ( $P < 0.05$ ).

Prior to LT, 105 patients (43.2%) had prolonged QTc. In 91 (86.7%), the mean QTc normalized after transplantation (baseline:  $490.9 \pm 45.74$  ms; post-transplantation  $385 \pm 48.74$  ms;  $P < 0.0001$ ). In 14 (13.3%) patients, some QTc shortening was noted, although QTc remained above the upper limit of normal. The prolonged QTc intervals in patients with cirrhosis appeared to be independent of the etiology of cirrhosis (Table 1). A normal QTc was

seen in 138 (56.7%) patients before transplantation. After surgery, the QTc remained normal in 134 (97.1%), whereas 4 (2.9%) developed QTc prolongation.

The mean QTd decreased significantly after LT (baseline:  $30 \pm 10$  ms; post-transplantation:  $30 \pm 20$  ms;  $P < 0.0001$ ; Figure 1).

The mean heart rate was  $72 \pm 8$  bpm pre-transplantation and  $69 \pm 6$  bpm post-transplantation.

## Discussion

Prolonged QTc interval was a common finding in our cirrhotic patients with subsequent normalization of QTc in the majority of patients after LT. These findings were similar to other reports.<sup>1,16,17</sup> A high prevalence of QTc prolongation was first noted in patients with alcoholic cirrhosis.<sup>16</sup> Alcoholic cirrhosis is the most common etiology in industrialized countries. In our study HBV was the most common cause of cirrhosis, although prolonged QTc intervals in our cirrhotic patients appeared to be independent of the etiology of cirrhosis. This implies that QTc prolongation in cirrhosis is related to the pathophysiology of cirrhosis itself and not reflective of an abnormality related to certain causes of cirrhosis.

According to some authors, the QTc interval prolongation in patients with cirrhosis may be an important marker for cirrhotic cardiomyopathy.<sup>15</sup> This entity involves chronic cardiac dysfunction, including systolic and diastolic changes, and electrophysiological abnormalities.

The cause of prolonged QTc in patients with advanced parenchy-

mal liver disease remains controversial. Prolonged QTc interval in cirrhotic patients may be related to autonomic neuropathy which also may cause reduced baroreflex sensitivity and heart rate variability.<sup>6,18,19</sup> In addition, chronotropic incompetence is a feature of autonomic neuropathy in these patients.<sup>20</sup> Autonomic dysfunction may play an important role in cirrhotic cardiomyopathy.

Questions remain regarding the clinical significance of QTd in chronic liver disease. It may be a predictor of ventricular arrhythmia and a negative prognostic factor in patients with cirrhosis. In our patients however, QTd had decreased significantly after LT, which is possibly promising.

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