doi: 10.5505/abantmedj.2014.00710

Abant Medical Journal

Orijinal Makale / *Original Article*

Volume Cilt 3 *Issue* Sayı 1 *Year* Yıl 2014

QT Dispersion Which Predicts Cardiovascular Adverse Event Risk, Increases In Non Alcoholic Fatty Liver Disease

Alkole Bağlı Olmayan Yağlı Karaciğer Hastalığında, Kardiyovasküler Riskin Öngördürücüsü Olan QT Dağılımı Artmıştır

Ahmet Oğuz Baktır[1], Bahadır Şarlı[1], Ahmet Karaman[2], Hüseyin Arınç[1], Hayrettin Sağlam[1], Hatice Karaman[3], Abdülsamed Erden[4], Yasemin Doğan[1]

[1]Kayseri Eğitim Ve Araştırma Hastanesi, Kardiyoloji Bölümü
[2]Kayseri Eğitim Ve Araştırma Hastanesi, Gastroenteroloji Bölümü
[3]Kayseri Eğitim Ve Araştırma Hastanesi, Patoloji Bölümü
[4]Kayseri Eğitim Ve Araştırma Hastanesi, İç Hastalıkları Bölümü

Özet

Amaç: Alkole bağlı olmayan yağlı karaciğer hastalığı ile kardiyovasküler morbidite ve mortalite arasındaki ilişki hızla artmaktadır. QT dağılımı (QTd) ve düzeltilmiş QT dağılımı (QTdz) ventrikül repolarizasyonunun heterojenitesini göstermektedir. Çeşitli kardiyovasküler hastalığı olan ve olmayan gruplarda artmış QTd ve QTdz'nin artmış kardiyovasküler riski öngördüğü gösterilmiştir. Ancak kaynak araştırmamıza göre, alkole bağlı olmayan yağlı karaciğer hastalığında QTd ve QTdz incelenmemiştir. Alkole bağlı olmayan yağlı karaciğer hastalığında meydana gelen myokardiyal hasar ile repolarizasyonunun anormalliği arasında ilişki olabileceğini varsaydık.

Yöntem: Gastroenteroloji polikliniğine başvurmuş ve alkole bağlı olmayan yağlı karaciğer hastalığı tespit edilmiş hastalar çalışmaya alındı.Yaş ve cinsiyet eşleşmesi yapılan sağlıklı kontrol bireyler ile QTd ve QTdz değerleri karşılaştırıldı.

Bulgular: Alkole bağlı olmayan yağlı karaciğer hastalığı tespit edilmiş hastalarda QTd (47.8±22.7 vs 22.5±7.5 ms, p<0,001) ve QTc (55.5± 28 vs 23.7±8.7 ms, p<0,001) değerlerinin kontrollerden anlamlı olarak yüksek olduğunu bulduk.

Sonuç: Alkole bağlı olmayan yağlı karaciğer hastalığı olan hastalarda oluşan repolarizasyon anormalliği hakkında bilinenler azdır. Uzamış QT dağılımı, alkole bağlı olmayan yağlı karaciğer hastalığında oluşabilecek klinik olarak tespit edilmemiş miyokard tutulumuna bağlı olabilir.

Anahtar Kelimeler: QT dağılımı, Alkole bağlı olmayan yağlı karaciğer hastalığı, kardiyovasküler risk.

Abstract

Objective: Association of cardiovascular morbidity and mortality with (non alcoholic fatty liver disease) NAFLD is increasing rapidly. The QT dispersion (QTd) and QT corrected dispersion (QTcd) reflects the heterogeneity of ventricular repolarisation.Predicting cardiovascular risk of an increased QTd and QTcd has been shown in various clinical cardiovascular and non cardiovasculer groups, but has not yet been studied in NAFLD patients according to our search of literature. We hypothesised that NAFLD related heart injury may cause myocardial repolarisation abnormalities.

Method: Forty five patients admitted to the department of gastroenterology outpatient clinic with the diagnose of NAFLD were included in this study. QT intervals were measured manually from the onset of QRS to the end of the T wave defined as a return to the T–P baseline.

Results: We found that QT dispersion (47.8±22.7 vs 22.5±7.5 ms, p<0.001) and QTc values (55.5± 28 vs 23.7±8.7 ms, p<0.001) were significantly higher in biobsy proven NAFLD patients without overt cardiac involvement than in control subjects.

Conclusion: Little is known about the possible myocardial repolarisation abnormalities NAFLD which are considered to be a risk factor for developing cardiovascular adverse events. Our study is the first to assess of myocardial repolarisation processes in NAFLD patients. Our result may indicate that prolonged QT dispersion can be a useful noninvasive and simple method of early detection of subclinical cardiac involvement in NAFLD patients.

Keywords: QT dispersion, non alcoholic fatty liver dısease, cardiovascular risk.

Giriş

Non alcoholic fatty liver disease (NAFLD) ranges from simple steatosis, steatohepatitis to advanced fibrosis and cirrhosis.(1) Association of cardiovascular morbidity and mortality with NAFLD is increasing rapidly.(2) Increased coronary risk scores, elevated levels of ox-LDL, prematüre atheroma formation, endothelial dysfunction, vulnerable coronary plaques and abnormal left ventricular energy metabolism are the basic reasons of this assosiation which shown in several cross-sectional studies. (3)

The QT dispersion (QTd) and QT corrected dispersion (QTcd) reflects the heterogeneity of

İletişim Bilgisi / Correspondence
Uzm. Dr. Ahmet Oğuz Baktır, Kayseri Eğitim Ve Araştırma Hastanesi, Kardiyoloji Bölümü / Kayseri
E-mail: a.oguz.baktir@tkd.org.tr

Geliş tarihi / *Received*: 09.07.2013 **Kabul tarihi / Accepted:** 21.08.2013 **Çıkar Çatışması / Conflict of Interest:** Yok / None

ventricular repolarisation and simply measured on a surface electrocardiography (ECG). Low cost and to be a non-invasive technique are the advatages. (4) Predicting cardiovascular risk of an increased QTd and QTcd has been shown in various clinical cardiovascular and non cardiovasculer groups, but has not yet been studied in NAFLD patients according to our search of literature. QTd and QTcd dispersion has been shown to be a marker of electrical instability and increased risk of sudden death and one of the assosiation is myocardial fibrosis. (5) It may contribute to cardiovascular marbidity and mortality as an additional cardiovascular risk predictor in NAFLD patients. We hypothesised that NAFLD related heart injury may cause myocardial repolarisation abnormalities.

Materyal ve Metod

Forty five patients admitted to the department of gastroenterology outpatient clinic with the diagnose of NAFLD were included in this cross-sectional study. Physical examination, past medical history of patients and blood biochemistry were evaluated in all groups to exclude systemic diseases. Patients with thyroid dysfunction, anemia, electrolyte imbalance, hypertension (HT), diabetes mellitus (DM), heart failure, rheumatic valve disease, primary cardiomyopathy, chronic lung disease, coronary artery disease, left bundle branch block and atrioventricular conduction abnormalities on ECG were excluded from the study. All of the patients were in sinus rhythm and none of them were taking medications like antiarrhythmics, antihistaminics, tricyclic antidepresants and antipsychotics. Sex and age matched tirty healthy volunteers were selected randomly for the control group.

Weight (kg) and height (m) were measured and BMI (kg/m2) was calculated. Blood pressure was measured in both of patient's arms using the first and the fifth phase of Korotkoff sounds with column mercury sphygmomanometry at rest in the sitting position. The 12-lead ECG was recorded by BioNet CardioCare 3000 (Bionet America, Inc.) at a paper speed of 50 mm/s and gain of 10 mm/mV in the supine position and were breathing freely but not allowed to speak during the electrocardiographic recording. We generally took the ECG recordings of all NAFLD patients and control subjects at the same time interval to avoid from diurnal variations. All of the ECGs were transferred to a digital storage via a scanner and then used for magnification of 200 times by Adobe Photoshop 5.5 software. QT intervals were measured manually from the onset of QRS to the end of the T wave defined as a return to the T–P baseline. (Fig. 1) If U waves were present, the subjects were excluded from the study. Three consecutive cycles in each of the leads were measured. QTc minimum and QTc maximum values were then calculated using Bazett's formula. (6)

All measurements were made by two experienced cardiologist blinded to the subjects' clinical status. From the three cycles, QT intervals were calculated. Dispersion parameters were calculated as the difference between maximal and minimal values of QT. The blinded inter and intra-observer variability of QT measurements were both <5%. Data were analysed with SPSS software version 16.0 for Windows (SPSS Inc, Chicago, Illinois, USA). Continuous variables are presented as mean ± SD. The Student's t-test was used to compare normally distributed continuous variables. A two-tailed p-value < 0.05 was considered statistically significant.

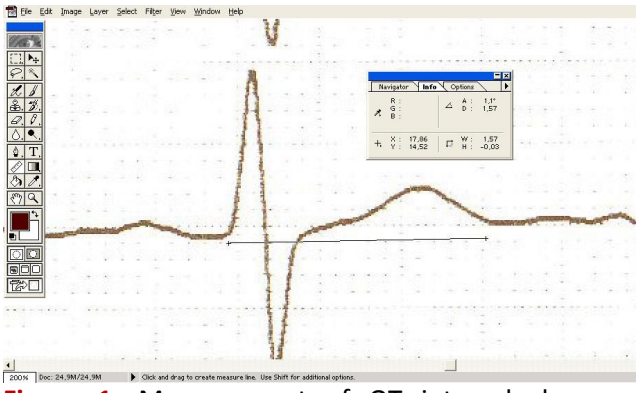

Figure 1. Measurement of QT intervals by Adobe Photoshop 5.5 software, manually from the onset of QRS to the end of the T wave defined as a return to the T–P baseline.

Bulgular

We studied fourty five NAFLD patients and 30 healthy control subjects (Mean age 42±10 vs 38±9, p=NS). The results of QTd and QTcd of the patients and the control group are shown in Table 1. There were no significant differences with respect to age. BMI (30.3 vs 23,5, p<0.001) and the homeostasis model assessment (HOMA) (5.22 vs 2.54, p<0.001) values were higher in NAFLD group. We found that QT dispersion (47.8±22.7 vs 22.5±7.5 ms, p<0.001) and QTc dispersion values (55.5± 28 vs 23.7±8.7 ms, p<0.001) were significantly higher in NAFLD patients than in control subjects.(Fig. 2)

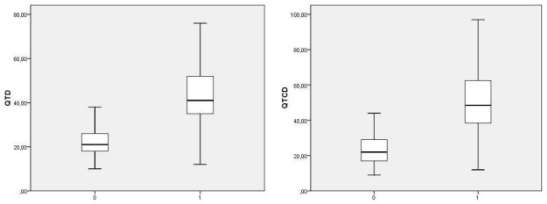

Figure 2. Significantly higher QT dispersion and QTc dispersion values in NAFLD patients than in control subjects.

Table 1. The results of QTd, QTcd, QTmin, QTmax, BMI, age and HOMA values of the patients and the control group.

	NAFLD	CONTROL	P VALUE
AGE	42,2	40,0	NS
BMI	30,3	23,5	<0,001
HOMA	5,22	2.54	<0,001
QTmax	377,6	384,1	NS
QTmin	329,9	361,5	<0,001
QTd	47,8	22,5	<0,001
QTcmax	426,5	400,3	=0,002
QTcmin	371,0	376,7	NS
QTcd	55,5	23,7	<0,001

BMI: Body Mass Index, HOMA: The Homeostasis Model Assessment; estimates steady state beta cell function and insulin sensitivity, QTd: QT dispersion, QTcd: QT corrected

Tartışma

Altough advanced left ventricular impairment can be dedected by conventional echocardiografic imaging, results may be normal at early stages of impairment. QTd and QTcd may be an other useful and simple marker to identify subclinical myocardial involvement in NAFLD patients. Therefore, we investigated QTd and QTcd values of NAFLD group with normal echocardiografic examination to dedect abnormalities of repolarisation as a result of acquired structural myocardial abnormalities. We found that QTd and QTcd values were higher in NAFLD group and the difference was statistically significant.

Cardiovascular morbidity and mortality in NAFLD patients are increasing rapidly due to assosiation of several clinical conditions like, increased coronary risk scores, elevated levels of ox-LDL, premature atheroma formation, endothelial dysfunction, vulnerable coronary plaques, left ventricular dysfunction and abnormal energy metabolism.(3) These were shown by several cross-sectional studies to be linked with cardiovascular morbidity and mortality in NAFLD patients.(2)

Higher QTd and QTcd favours the development of serious and life-threatening adverse effects via ventricular arrhythmias and to be an important prognostic factor was shown in patients with various cardiac conditions, such as coronary artery disease, congestive heart failure, and cardiomyopathies. (5,7,8) Altough rate correction of parameters of dispersion of repolarization has been shown by some reports unnecessary, we investigated both QTd and QTcd because of debate on this topic. (9) And both QTd and QTcd values were higher in patients with NAFLD.

The main pathophysiological mechanism of NAFLD is insulin resistance (IR). The impairment of insulin action in the liver, skeletal muscle, and adipose tissue of obese subjects are constituted by the increase in intrahepatic triglycerides (IHTG). (10-12) Especially, in diabetic patients liver fat content independently indicates myocardial IR and impaired coronary functional capacity. (13) Framingham Heart Study has also reported that IHTG content predicts the glucose and lipid abnormalities of the metabolic syndrome

independent of visceral fat.(14,15) Hepatic steatosis is associated with hepatic IR and impaired suppression of hepatic glucose production, which leads to hyperglycemia, compensatory hyperinsulinemia and consequently worsening of systemic and cardiac IR. Thus, hepatic IR may be a possible link between NAFLD and altered cardiac energy metabolism. These data suggests that NAFLD may be actively involved in the onset and progression of cardiovascular disease.

Cardiac lipotoxicity is a well described phenomenon in IR, and is generally attributed to products of free fatty acids (FFA) excess metabolism. (16) Hepatic fat content may represent an indicator of a systemic condition of ectopic triglyceride accumulation, involving the cardiac structures. Despite the resulting damage is different, heart and liver share common mechanisms of lipotoxicity. In the heart, ceramide accumulation formed via de novo synthesis from FFA, plays a central role in apoptosis of cardiomyocytes. Structural alterations in mitochondria can reduce cardiac function by providing an insufficient supply of ATP to cardiac myocytes or by increasing reactive oxygen species (ROS) production, which has been associated with increased apoptosis, DNA damage, and decreased DNA repair. (17) The increased level of FFA in the liver causes FFA oxidation and increases the production of free radicals leading to lipoperoxidation, DNA and protein damage, endogenous antioxidants depletion and mitochondrial damage.(18) As in the liver, cardiac lipotoxicity occurs by increasing ROS and RNS production, which leads to DNA damage and death of myocardiocytes. (19,20) In patients with nonischemic chronic heart failure with obesity and/or diabetes, lipotoxicity plays an essential role in the pathogenesis of cardiomyopathy which is a leading cause of death.(19-21) Human and rodent models indicated that myocardial triglyceride content was directly related to the degree of myocardial dysfunction (22).
Myocardial fat causes alterations in cardiac work and myocardial oxygen consumption which leads to impaired ventricular contractility. (21,22) Impaired ventricular contractility because of early left ventricular dysfunction and impaired energetics may be dedected by advanced echocardiographic features and magnetic resonance spectroscopy in NAFLD patients without obesity, hypertension and diabetes. (23) The areas of myocardial fibrosis in NAFLD may disrupt the course of ventricular repolarization and lead to increase the dispersion of recovery time throughout the ventricle. As QT dispersion proves useful information of heterogeneity of ventricular repolarization, prolonged QTd and QTcd that we found in our study may reflect silent myocardial involvement in NAFLD patients. Fibrosis of the myocardium may be responsible for the repolarisation abnormalities in the NAFLD patients and help to explain higher QTd and QTcd compared to controls as in our study.

According to these data, in clinical settings QTd and QTcd may reflect silent myocardial dysfunction, due to mentioned pathophysiological mechanisms in NAFLD patients without clinical cardiac manifestations. At early stages some of the myocardial changes might not have been detected in the conventional echocardiografic examination, but would be visible by QTd and QTcd like MRI, or revealed in biopsy. (24) In our study, the patients with NAFLD were more obese then the control group, but did not have morbid obesity. They also had blood pressure levels that were within normal limits and equal to that of the controls.

To the best of our knowledge, this is the first study evaluating the QTd and QTcd in patients with NAFLD. We found that QT dispersion is significantly higher in patients with NAFLD than in control subjects. Little is known about the possible myocardial repolarisation abnormalities in NAFLD which are considered to be a risk factor for developing cardiovascular adverse events. Our study is the first to assess of myocardial repolarisation processes in NAFLD patients. The QTd measurement is a simple, non-invasive and lowcost method of assessing the heterogeneity of myocardial repolarisation. (25)

Conclusion

QT dispersion is significantly increased in NAFLD patients without overt cardiac involvement. Our result may indicate that prolonged QT dispersion can be a useful noninvasive and simple method of early detection of subclinical cardiac involvement in NAFLD patients. Further studies are needed to evaluate the prognostic significance of QT dispersion and to clarify the mechanism of increased QT dispersion in NAFLD.

Kaynaklar

1-Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005; 128: 1898–906.

2-Bugianesi E. Nonalcoholic fatty liver disease (NAFLD) and cardiac lipotoxicity: Another piece of the puzzle. Hepatology 2008; 47: 2–4.

3-Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology. 2009; 49: 306–17.

4-JC, Molnar J. Usefulness of QT dispersion as an electrocardiographically derived index. Am J Cardiol, 2002; 89: 291–29

5-Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. Lancet 1994; 343: 327–329.

6-Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 2001; 26: 321-31

7-Sevimli S, Arslan S, Gündoğdu F. Carvedilol therapy is associated with improvement in QT dispersion in patients with congestive heart failure. Arch Turk Soc Cardiol 2007; 35:284-288.

8-Glancy JM, Garratt CJ, Woods KI, Bono DP. QT dispersion and mortality after myocardial infarction. Lancet 1995; 345: 945–948.

9-Zabel M, Woosly RL, Franz MR. Is dispersion of ventricular repolarisation rate dependent? PACE 1997; 20(Part I): 2405–2411.

10-Korenblat KM, Fabbrini E, Mohammed BS, Klein S. Liver, muscle, and adipose tissue insulin action is directly related to intrahepatic triglyceride content in obese subjects. Gastroenterology 2008; 134: 1369–75.

11-Korenblat KM, Fabbrini E, Mohammed BS, Klein S. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proc Natl Acad Sci USA 2009; 106: 15430–5.

12-Salamone F, Bugianesi E. Nonalcoholic fatty liver disease: the hepatic trigger of the metabolic syndrome. J Hepatol 2011; 53: 1146–7.

13-Lautamäki R, Borra R, Iozzo P, Komu M, Lehtimäki T, Salmi M, Jalkanen S, Airaksinen KE, Knuuti J, Parkkola R, Nuutila P. Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. Am J Physiol Endocrinol Metab 2006; 291: 282–90.

14-Speliotes EK, Massaro JM, Hoffmann U, Vasan RS, Meigs JB, Sahani DV, Hirschhorn JN, O'Donnell CJ, Fox CS. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: the Framingham Heart Study. Hepatology 2010; 51: 1979–87.

15-Salamone F, Galvano F, Li Volti G. Treating fatty liver for the prevention of cardiovascular diseases. Hepatology 2010; 52: 1174–5.

16-Unger RH, Orci L. Lipotoxic diseases of nonadipose tissues in obesity. IntJ Obes Relat Metab Disord 2000; 24: 28-S32.

17-Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation 2007; 115: 3213-3223.

18-Mantena SK, King AL, Andringa KK, Eccleston HB, Bailey SM. Mitochondrial dysfunction and oxidative stress in the pathogenesis of alcohol and obesity induced fatty liver diseases. Free Radic Biol Med 2008; 44: 1259–72.

19-Marra F. Nuclear factor-kappaB inhibition and non-alcoholic steatohepatitis: inflammation as a target for therapy. Gut 2008; 57: 570–2.

20-Mellor KM, Ritchie RH, Delbridge LM. Reactive oxygen species and insulinresistant cardiomyopathy. Clin Exp Pharmacol Physiol 2010; 37: 222–8.

21-McGavock JM, Victor RG, Unger RH, Szczepaniak LS. Adiposity of the heart, revisited. Ann Intern Med 2006; 144: 517–24.

22-Neubauer S. The failing heart an engine out of fuel. N Engl J Med 2007; 356: 1140–51.

23-Perseghin G, Lattuada G, De Cobelli F, Esposito A, Belloni E, Ntali G, Ragogna F, Canu T, Scifo P, Del Maschio A, Luzi L. Increased mediastinal fat and impaired left ventricular energy metabolism in young men with newly found fatty liver. Hepatology 2008; 47: 51–8.

24-Szczeklik W, Sokolowska B, Mastalerz L, Miszalski-Jamka T, Musial J. Heart involvement detected by magnetic resonance in a patient with Churg-Strauss syndrome, mimicking severe asthma exacerbation. Allergy. 2010; 65: 1063–1064

25-Somberg JC, Molnar J. Usefulness of QT dispersion as an electrocardiographically derived index. Am J Cardiol 2002; 89: 291–294.