Increased QT dispersion and P wave dispersion in major depressive disorder

Aydın Rodi Tosu MD[1], Serafettin Demir MD[2], Yüksel Kaya MD[3], Murat Selcuk MD[1], Müntecep Asker MD[1], Mahmut Özdemir MD[4], Erhan Tenekecioglu MD[5]

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BACKGROUND: QT and P wave dispersion parameters can indicate abnormalities in autonomic nervous system and cardiac functioning.
OBJECTIVES: To determine QT and P wave dispersion in patients with major depressive disorder compared with healthy volunteers.
METHODS: Fifty newly diagnosed patients with major depressive disorder and 50 age- and sex-matched healthy volunteers underwent 12-lead electrocardiography. QT interval, QT dispersion, heart rate-corrected QT dispersion and P wave dispersions were calculated manually by a blinded specialist.
RESULTS: Groups were comparable in terms of age, sex, body mass index, smoking status, metabolic diseases and left ventricular ejection fraction. The major depressive disorder group had significantly higher QT dispersion (58.5±9.9 versus 41.7±3.8; P<0.001), heart rate-corrected QT dispersion (62.5±10.0 versus 45.2±4.3; P<0.001) and P wave dispersion (46.9±4.8 versus 41.5±5.1; P<0.001).
CONCLUSION: Increased QT dispersion, heart-rate corrected QT dispersion and P wave dispersion in major depressive disorder patients may be indicative of autonomic imbalance and increased risk of cardiac morbidity and mortality.

Key Words: *Autonomic nervous system; Cardiac function; Cardiovascular diseases; Depression; Electrocardiography*

Major depressive disorder (MDD) is a common disease with a lifetime prevalence of 14.6% in high-income countries and 11.1% in middle or low income countries (1). Several epidemiological studies have shown that clinical depression and depressive symptoms are important risk factors for cardiovascular disease (CVD) and cardiovascular mortality, both in patients with (2-4) and without preexisting CVD (5-8).

The relationship between CVD and depression is multifaceted and bidirectional (9). Dysregulation of the autonomic nervous system (ANS) is believed to be one of the mechanisms linking depression to cardiovascular events. In particular, decreased heart rate variability has received much attention as an important marker of ANS imbalance in depression and CVD (10-13).

QT interval dispersion (QTD), defined as QT interval time variation between electrocardiograms (ECG) recorded on different leads, is a noninvasive measure of ventricular repolarization abnormalities. Similar to heart rate variability, QTD is associated with ANS imbalance, and it has been shown to increase in response to decreased parasympathetic tone in healthy subjects (14). In two large prospective studies involving middle-age or elderly individuals, elevated QTD was found to be associated with increased risk of overall mortality and cardiovascular mortality (15,16), while in another large prospective study it found to be associated with stroke mortality (17).

P wave dispersion (PD), defined as the time difference between the maximum and minimum of the P wave on 12-lead ECG, is a noninvasive marker of disorganized atrial repolarization, and was proposed to be used as a predictor of atrial fibrillation (18-21).

In the present study, we aimed to determine QTD and PD in MDD patients compared with healthy volunteers, as predictors of cardiovascular morbidity or mortality.

METHODS

The present case-control study was conducted in the psychiatry department of Van Training and Research Hospital (Van, Turkey) between 2010 and 2012. A total of 50 patients diagnosed with MDD for the first time at the outpatient psychiatry clinic of the hospital and 50 age- and sex-matched physically and mentally healthy volunteers were included in the study. Patients with underlying cardiac conditions, abnormal ECG findings, or taking antidepressants or other medication use that may interfere with ECG results were excluded. The study was approved by the local ethics committee and written informed consent was obtained from all subjects.

Electrocardiographic calculations

Standard 12-lead ECG 50 mmV recording was performed following a 10 min rest in the supine position. The QT interval, QTD and PD calculations were performed manually by a blinded specialist. The QT interval was measured from the onset of the QRS complex to the end of the T wave. In the case of a U wave, the end of the T wave was accepted as the nadir between T and U waves. The mean of three consecutive interval measurements was used in the analysis. QTD was calculated as the difference between the maximum and the minimum intervals. Heart rate-corrected QT dispersion (QTcD) was defined as the QTD with heart rate correction, according to Bazett's formula (22). The P wave was measured from the first sign of upward departure from the baseline to the point of return to the baseline. PD was defined as the difference between the maximum and minimum of the P waves measured in any of the 12 leads.

Statistical analysis

SPSS version 15.0 (IBM Corporation, USA) for Windows (Microsoft Inc, USA) was used for the statistical analysis. Descriptive statistics were expressed as mean ± SD or frequencies. Group means were compared using either the Mann-Whitney U test or independent samples Student's *t* test. Categorical variables were compared using Pearson's χ^2 test; P<0.05 was considered to be statistically significant.

RESULTS

Demographic and clinical characteristics of MDD patients and healthy volunteers are presented in Table 1. There was no significant difference between the groups in terms of age, sex, body mass index, smoking status, metabolic diseases and left ventricular ejection fraction (Table 1).

[1]*Department of Cardiology, Van Training and Research Hospital, Van;* [2]*Department of Cardiology, Adana State Hospital, Yüreğir, Adana;* [3]*Department of Cardiology, Kafkas University, Kars;* [4]*Department of Cardiology, Yüzüncü Yıl University Medical Faculty, Van;* [5]*Department of Cardiology, Bursa Yuksek Ihtisas Education and Research Hospital, Bursa, Turkey*
Correspondence: Dr Şerafettin Demir, Adana Devlet Hastanesi Karataş Yolu Yüreğir/Adana, Turkey. Telephone 90-533-627-19-91, fax 90-332-332-83-30, e-mail demirkardiyoloji@hotmail.com

TABLE 1
Demographic and clinical characteristics of the patients

	Control (n=50)	MDD (n=50)	P
Age, years	39.8±5.3	38.5±4.3	0.055
Sex, men/women	18/32	20/30	0.680
Body mass index, kg/m^2	24.4±1.9	24.5±1.7	0.922
Smoker	35	35	1.000
Hypertension	1	2	–
Diabetes	0	1	–
Hyperlipidemia	2	1	–
LVEF, %	60.5±2.2	60.8±1.4	0.171
Na^+, mEq/L	138.8±4.3	138.9±4.0	0.276
K^+, mEq/L	4.6±0.7	4.5±0.7	0.342
Mg^{2+}, mg/dL	1.9±0.4	1.9±0.3	0.126
Ca^{2+}, mg/dL	9.2±0.7	9.3±0.7	0.185

Data are presented as mean ± SD unless otherwise indicated. MDD Major depressive disorder; LVEF Left ventricular ejection fraction

MDD patients had significantly higher QTD (58.5±9.9 versus 41.7±3.8; P<0.001), QTcD (62.5±10.0 versus 45.2±4.3; P<0.001) and PD (46.9±4.8 versus 41.5±5.1; P<0.001) compared with the control group (Table 2).

Women had higher PD compared with men (45.1±6.3 versus 42.6±3.8; P=0.015), while QTD and QTcD were not significantly different between men and women. Smoking status, age and body mass index did not significantly affect QTD, QTcD or PD.

DISCUSSION

In the present study, we showed that nonmedicated patients with a first-time diagnosis of MDD had significantly higher QTD, QTcD and PD compared with age- and sex-matched healthy volunteers.

QTD and QTcD were previously investigated in a small-scale study. Nahshoni et al (23) measured QTD and QTcD in a group of 18 elderly patients with recurrent MDD maintained on antidepressant medication and showed that they had significantly higher QTD and QTcD compared with nine age- and sex-matched healthy subjects. Our results support and extend their findings in a larger group of MDD patients. Because our patients were not using antidepressant medication at the time of ECG measurements, drug side effects can be eliminated as a potential cause of ANS imbalance in these patients. Furthermore, our analysis shows that QTD is affected even in younger or middle-age patients at or near the beginning of their first-ever major depressive episode, suggesting that the toll of stress on the cardiovascular system is immediate. However, at this time we cannot rule out the possibility that elevated QTD could also be a trait marker of depressive personality.

Two studies measured QTD of MDD patients in relation to the effects of electroconvulsive therapy. Tezuka et al (24) noticed that MDD patients had high QTD at baseline and that QTD peaked immediately after electroconvulsive therapy and returned to baseline within 5 min to 6 min. In a follow-up study they showed that older and younger patients had similar QTD at baseline but QTD was increased significantly more in older patients during the 7 min following electroconvulsive therapy (25) Although these studies focused on the effects of electroconvulsive therapy and did not include a control group, their observation of high baseline QTD in MDD patients is consistent with our results. It would be interesting to determine whether QTD would further decrease to normal levels in successfully treated MDD patients.

To the best of our knowledge, ours is the first study to show elevated PD in MDD patients compared with a control group. PD was assessed in 30 MDD patients undergoing electroconvulsive therapy and a significant increase in PD was observed after the shock compared with the baseline reading (26). However, in this study there was no control group to determine the difference at baseline.

TABLE 2
Mean QT and P dispersion on 12-lead electrocardiographic recording of control and major depressive disorder (MDD) groups

	Control	MDD	P
QTD	43.6±3.7	58.8±9.5	<0.001
QTcD	44.3±5.1	61.5±9.1	<0.001
PD	42.4±5.3	46.2±5.6	<0.001

Data are presented as mean ± SD unless otherwise indicated. PD P wave dispersion; QTcD Heart rate-corrected QT interval dispersion; QTD QT interval dispersion

There are some limitations to the present study. QT interval measurement is affected by factors such as low T wave amplitude, T wave merging with P or U waves and abnormal morphology of T wave (27). Consequently, intraobserver and interobserver variability is often high with QTD measurements. We tried to overcome this problem by having a single blinded expert performing all measurements methodically. Because computerized dispersion calculations were not shown to be superior to manual calculations, we opted for manual measurement (28).

Heart rate correction of QTD is controversial. Current belief dictates that heart rate does not modify QTD and that QTD should not be corrected for heart rate (27). Although we calculated QTcD in our study, the results paralleled QTD and did not affect the interpretation of our results.

Limitations

Potential limitations to the present study include the relatively small sample size and the fact that there is no supporting evidence, such as a biomarker, 24 h Holter or 24 h ambulatory blood pressure monitoring, that would show conclusively that the reason for correlation is indeed ANS disturbances.

CONCLUSION

Our study shows increased PD, QTD and QTcD in patients newly diagnosed with MDD, suggesting a link between ANS imbalance and depression. Further studies are warranted to show a causative link between these ECG parameters and cardiovascular morbidity and mortality in MDD.

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REFERENCES

1. Bromet E, Andrade LH, Hwang I, et al. Cross-national epidemiology of DSM-IV major depressive episode. BMC Med 2009;9:90.
2. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. Psychosom Med 66:2004;802-13.
3. de Jonge P, Spijkerman TA, van den Brink RH, Ormel J. Depression after myocardial infarction is a risk factor for declining health related quality of life and increased disability and cardiac complaints at 12 months. Heart 2006;92:32-9.
4. Horsten M, Mittleman MA, Wamala SP, Schenck-Gustafsson K, Orth-Gomer K. Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. Eur Heart J 2000;21:1072-80.
5. Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML. Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey. Arch Intern Med 2000;160:1261-8.
6. Janszky I, Ahlbom A, Hallqvist J, Ahnve S. Hospitalization for depression is associated with an increased risk for myocardial infarction not explained by lifestyle, lipids, coagulation, and inflammation: The SHEEP Study. Biol Psychiatry 2007;62:25-32.
7. Penninx BW, Beekman AT, Honig A, et al. Depression and cardiac mortality: Results from a community-based longitudinal study. Arch Gen Psychiatry 2001;58:221-7.

8. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. Int J Geriatr Psychiatry 2007;22:613-26.
9. Lippi G, Montagnana M, Favaloro EJ, Franchini M. Mental depression and cardiovascular disease: A multifaceted, bidirectional association. Semin Thromb Hemost 2009;35:325-36.
10. Krittayaphong R, Cascio WE, Light KC, et al. Heart rate variability in patients with coronary artery disease: Differences in patients with higher and lower depression scores. Psychosom Med 1997;59:231-5.
11. Stein PK, Carney RM, Freedland KE, et al. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. J Psychosom Res 2000;48:493-500.
12. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. Biol Psychiatry 2010;67:1067-74.
13. Taylor CB. Depression, heart rate related variables and cardiovascular disease. Int J Psychophysiol 2010;78:80-8.
14. Ishida S, Nakagawa M, Fujino T, Yonemochi H, Saikawa T, Ito M. Circadian variation of QT interval dispersion: Correlation with heart rate variability. J Electrocardiol 1997;30:205-10.
15. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. QTc dispersion predicts cardiac mortality in the elderly: The Rotterdam Study. Circulation 1998;97:467-72.
16. Okin PM, Devereux RB, Howard BV, Fabsitz RR, Lee ET, Welty TK. Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians: The Strong Heart Study. Circulation 2000;101:61-6.
17. Perkiomaki JS, Sourander LB, Levomaki L, Raiha IJ, Puukka P, Huikuri HV. Qt dispersion and mortality in the elderly. Ann Noninvasive Electrocardiol 2001;6:183-92.
18. Chandy J, Nakai T, Lee RJ, Bellows WH, Dzankic S, Leung JM. Increases in P-wave dispersion predict postoperative atrial fibrillation after coronary artery bypass graft surgery. Anesth Analg 2004;98:303-10.
19. Dilaveris PE, Gialafos JE. P-wave dispersion: A novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol 2001;6:159-65.
20. Perez MV, Dewey FE, Marcus R, et al. Electrocardiographic predictors of atrial fibrillation. Am Heart J 2009;158:622-8.
21. Rosiak M, Bolinska H, Ruta J. P wave dispersion and P wave duration on SAECG in predicting atrial fibrillation in patients with acute myocardial infarction. Ann Noninvasive Electrocardiol 2002;7:363-8.
22. Bazzett H. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353-70.
23. Nahshoni E, Aravot D, Aizenberg D, et al. QT dispersion in the surface electrocardiogram in elderly patients with major depression. J Affect Disord 2000;60:197-200.
24. Tezuka N, Egawa H, Fukagawa D, et al. Assessment of QT interval and QT dispersion during electroconvulsive therapy using computerized measurements. J ECT 2010;26:41-6.
25. Yamaguchi S, Nagao M, Ikeda T, et al. QT dispersion and rate-corrected QT dispersion during electroconvulsive therapy in elderly patients. J ECT 2011;27:183-8.
26. Aydin A, Gumrukcuoglu HA, Selvi Y, et al. Alterations in P wave duration and dispersion in depressive patients following electroconvulsive therapy. Gen Hosp Psychiatry 2012;34:201-5.
27. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. J Am Coll Cardiol 2000;36:1749-66.
28. Kors JA, van Herpen G. Measurement error as a source of QT dispersion: A computerised analysis. Heart 1998;80:453-8.