European Journal of
Human Health

ORIGINAL ARTICLE

Pathological Q Wave in Electrocardiographic Examinations of Patients with Schizophrenia

Selcuk KANAT [1], Hakan DEMIRCI [2], Ufuk AYDIN [3], Ibrahim TAYMUR [4], Fatih CIFTCI [5], Emre YALCINTAS [6], Gokhan OCAKOGLU [7], Erhan TENEKECIOGLU [1]

[1] Department of Cardiology, University of Health Sciences Turkey Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, TURKEY
[2] Department of Family Medicine, University of Health Sciences Turkey Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, TURKEY
[3] Department of Cardiovascular Surgery, University of Health Sciences Turkey Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, TURKEY
[4] Department of Psichiatry, University of Health Sciences Turkey Bursa Yuksek İhtisas Training and Research Hospital, Bursa, TURKEY
[5] Istiklal Family Health Center, Bursa, TURKEY
[6] Mutareke Family Health Center, Bursa, TURKEY
[7] Department of Biostatistics, Uludag University Medical Faculty, Bursa, TURKEY

01

ABSTRACT

Aim: The aim of our study was to investigate the frequency of the ischemic and proarrhythmic electrocardiographic (ECG) changes in schizophrenia patients compared to normal healthy population.

Methods: This study was planned retrospectively. ECG documents were obtained from the first day of admission to patients' psychiatric clinic. The study involved 190 hospitalized schizophrenia patients and 134 healthy controls. The rhythm of the patient, presence of channelopathy, hypertrophy findings of cardiac cavities, conduction defects, ischemic changes, p-wave length, p-wave dispersion (PWD), the presence of fragmented QRS (fQRS), QT dispersion were considered in the ECG records.

Results: The mean systolic and diastolic blood pressure were higher in the control group ($p<0.001$). Smoking was more prevalent among patients with schizophrenia. The heart rate was higher in the schizophrenia group than control group (85.5 vs 70.5 beats/min;$p<0.001$). QT-dispersion time was also higher in the schizophrenia group (35 milliseconds versus 55 milliseconds; $p<0.001$). P-wave dispersion time was found higher in schizophrenia group (30 to 47.50 milliseconds, $p<0.001$). The incidence of fragmented QRS (fQRS) was 36.30% (n: 69) in the schizophrenic group and 7.5% (n:10) in the healthy control group ($p=0.001$). Pathological Q-wave frequency was about 10 times higher in patients with schizophrenia ($p<0,001$).

Conclusions: The proarrhythmic and ischemic electrocardiographic changes may explain the high frequency of premature deaths seen in patients with schizophrenia. When psychiatrists evaluate schizophrenia patients, they should be aware of these cardiac findings and should be in close contact with cardiologists as necessary.

Keywords: Dysrhythmia, pathological Q-wave, p-wave dispersion, fragmented QRS, schizophrenia

Corresponding Author: Selçuk KANAT drselcukkanat@gmail.com

Received: ***December 12, 2021;*** *Accepted:* ***April 25, 2022;*** *Published Online:* ***April 30, 2022***

Cite this article as: Kanat, S., Demirci, H., Aydin, U. , Taymur, I., Ciftci, F., Yalcintas, E., & Tenekecioglu, E. (2022). Pathological Q Wave in Electrocardiographic Examinations of Patients with Schizophrenia. European Journal of Human Health 2(1), 1-11.

Introduction

Cardiovascular disease is the most common cause of mortality in patients with schizophrenia. In recent years, an increase of one third has been reported in the relative risk of mortality associated with coronary artery disease (CAD) in schizophrenia (1). Among the common causes of cardiovascular deaths, arrhythmias, such as atrial fibrillation (AF), ventricular tachycardia and torsade de pointes, as well as myocardial infarction (MI) have considerable prevalence(2, 3).

The increase in the frequency of cardiac disease in schizophrenia patients is associated with several factors, in particular smoking, obesity, diabetes, dyslipidemia, metabolic syndrome, sedentary lifestyle, decreased self-care and antipsychotic drug usage (4). Severity of positive and negative symptoms of the disease, accompanying neuro-cognitive disorders and low social functioning destroy the ability of schizophrenia patients to recognize cardiac symptoms, to notify their complaints to the treatment team and to adapt to the treatment (5).

Electrocardiography (ECG) is a safe, noninvasive first line diagnostic tool for evaluating cardiovascular disorders. Hemodynamic changes in schizophrenia patients can lead to some alterations in ECG. These are heart rate increment, prolonged corrected QT interval (QTc), inversion of T-waves and left axes deviation of QRS. P-wave dispersion (Pd), which is an ECG marker associated with a heterogenous and non-sustained distribution of the sinus impulse, has shown to be a predictor for prolonged inter-atrial and intra-atrial conduction. Increased Pd values were associated with an increased risk of atrial fibrillation (6). Another parameter that can be defined as the difference between the maximal and minimal QT interval measured in many ECG leads is QT dispersion (QTd). QT interval parameters especially heart-rate corrected QT (QTc) interval, are presumed as cardiovascular risk factor (7). QTd is an indicator for the non-homogeneity of myocardial repolarization. Fragmented QRS (fQRS) is an ECG finding in patients with myocardial scar through altered ventricular depolarization. fQRS is more sensitive than pathological Q-waves in detection of myocardial fibrosis detected by Single-photon emission computed tomography (SPECT) imaging in CAD (8).

In schizophrenia, an increase in heart rate, QTc prolongation, ventricular arrhythmia and cardiac arrest have been reported. The risk of sudden cardiac death in patients using antipsychotics is 2.4 fold higher (9). The arrhythmogenic effects of antipsychotic drugs are delayed ventricular depolarization and repolarization, conduction disorders, sinus node abnormalities and sinus tachycardia developing as a response to postural hypotension (9). The underlying pathophysiology of such side effects of the antipsychotics are anticholinergic effects, α1 antagonistic features and blockage of potassium channels in myocardium (10-13).

An increased risk of cardiovascular disease in schizophrenic patients has been clearly defined. However, our knowledge about ECG changes, in particular ischemic changes, in patients with schizophrenia is limited. The aim of the present study was to investigate the frequency of atrial and ventricular pro-arrhythmic and ischemic ECG changes in schizophrenia patients compared to the healthy subjects.

Methods

Study Population

The current study was conducted retrospectively by reviewing the records of patient files. The study involved 190 schizophrenia patients who received inpatient treatment in a psychiatry clinic between

2018-2019. One hundred thirty-four healthy subjects were recruited as control group. ECG was recorded during the first day of hospitalization. A 12-lead ECG recording was taken from all of the patients and from the control group (n=324).

The medications of the schizophrenia patients prior to their hospitalization were noted. The patients with systemic cardiac disease, rheumatic heart disease, pre-excitation syndrome, heart failure, patients with a permanent pacemaker and patients using anti-arrhythmic drug were excluded from the study.

ECG assessment

ECGs were recorded in decubitus position and eupnea status, while the patients were not allowed to cough or talk. During ECG recording , the recorder was adjusted to a speed of 50 mm/ sec, calibration of 1mV/cm, filter to 100 Hz and alternative current filter to 60 Hz. ECG records were taken manually by two researchers who were not informed for the clinical status of the subjects.

The rhythm of the patient, signs of channelopathy, ECG finding of myocardial hypertrophy, any conduction defect, ischemic changes, p-wave times, Pd, presence of fQRS, QT/cQT durations and QT dispersion were noted during ECG recordings.

The P-wave duration in ECG was calculated by measuring the distance between the intersection of the beginning of P-wave deflection and the isoelectric line and the intersection of the P-wave and the isoelectric line. P-wave durations were measured through all leads. After P maximum (Pmax) was defined as the longest measurable P-wave duration whereas P minimum (Pmin) was the shortest one. Pd was calculated as the difference between maximum and minimum P-wave durations (Pd= Pmax-Pmin).

In ECG, the distance between the beginning of the QRS complex and the intersection point of the T-wave descent with isoelectric TP-segment was recorded as the QT interval. The QT corrected (QTc) according to heart rate was calculated with the Bazett formula [QT(msec)/ RR (sec)1/2]. In patients with U-waves, QT was calculated to the lowest point of the curve between the T- and U-waves. QTc maximum (QTc max) and QTc minimum (QTc min) were defined as the longest and the shortest measurable QT-interval durations, respectively. QTc dispersion (QTc disp) was calculated as the maximum minus minimum QTc durations (QTc disp= QTc max- QTc min).In ECG, fQRS was described as notching of the R-wave in two neighboring derivations, notching in the S-wave, existence of an RSR' pattern or more than one R' -wave (8, 14-18).

All ECG analysis was performed by two experienced cardiologist blinded to patients data. A magnifying lens and a caliper was used to define the ECG deflections. The intra and interobserver coefficients of variations were calculated to check the reproducibility of the analysis.

Statistical Analysis

Data were expressed as mean ± standard deviation (minimum: maximum) or median (IQR: Inter-quartile Range) values depending on whether the variable followed a normal distribution using the Shapiro-Wilk normality test. For comparisons of continuous variables between groups, independent samples t-test and Mann Whitney-U test were performed. Comparisons of categorical variables were done using Chi-square, Fisher's exact test and Fisher-Freeman-Halton tests. To determine independent risk factors those affected schizophrenia, binary logistic regression analysis (with Forward LR method) was performed after univariate analysis. The results of the final model were reported with related odds ratio (95% confidence

interval) values with respective p-values. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version20.0. Armonk, NY: IBM Corp.).

Ethics

The ethical approval for the study was obtained from local ethics committee in our institution.

Results

Patient characteristics are shown in Table-1. Smoking was significantly more prevalent in patients with schizophrenia ($p<0.001$). Both systolic and diastolic blood pressure values were higher in the control group compared to the patients with schizophrenia.

Table1. Comparisons of the general characteristics of the study groups

	Controls (n=134)	Patients with schizophrenia (n=190)	p-value
Age (years)	39.51±13.07 (20:82)	39±14.46 (18:84)	0.747
Gender (f/m)	66/68	74/116	0.065
Smoking	35/134	106/190	0.001
Systolic Blood Pressure	122.69±20.30 (85:195)	113.89±11.57 (90:150)	0.001
Diastolic Blood Pressure	75.04±12.83 (50:118)	71.63±8.09 (50:90)	0.004

Comparison of ECG findings between the study groups is demonstrated in Table-2. In the schizophrenia group, HR level, QRS width, Pmax, P-dispersion and QT dispersion were higher than the control group. In the control group, the level ofP-min and the QT level were higher in the schizophrenia group. The fQRS, left anterior hemiblock (LAHB), ST depression and pathological Q-wave incidence were higher in patients with schizophrenia.

Table2. Comparison of ECG findings of the patient and control groups

	Controls (n=134)	Patients with schizophrenia (n=190)	p-value
Heart Rate (per minute)	70.50 (15)	85.50 (25)	<0.001
QRS width	80 (26.50)	84.50 (15)	0.022

PR length	150 (25)	145 (30)	0.065
P-maximum duration	86.91±16.44 (50:130)	94.19±18.38 (55:160)	<0.001
P-minimum duration	60 (15)	40 (10)	<0.001
P-dispersion	30 (20)	47.50 (20)	<0.001
QT length	375 (30)	360 (54.50)	0.019
cQT	410 (23.50)	406 (31.50)	0.943
QT dispersion	35 (10)	55 (25)	<0.001
Sinus Arrhythmia*	14 (10.40%)	19 (10%)	0.896
fQRS*	10 (7.50%)	69 (36.30%)	<0.001
Ventricular premature beats*	0	2 (1.10%)	0.513
Supraventricular ectopic beats*	1 (0.70%)	1 (0.50%)	1.00
Early Repolarization	8 (6%)	10 (5.30%)	0.784
Left Bundle Branch Block*	0	1 (0.50%)	1.00
Left anterior hemiblock*	0	6 (3.20%)	0.044
Left posterior hemiblock*	0	0	NA
Tri-fascicular Block*	0	0	NA
ST depression*	0	7 (3.70%)	0.044
Ischemic T*	0	2 (1.10%)	0.513
Pathological Q*	2 (1.50%)	22 (11.60%)	<0.001
Left Ventricular Hypertrophy*	3 (2.20%)	9 (4.70%)	0.372
Right ventricular hypertrophy*	0	1(0.50%)	1.00
Right atrium enlargement *	1 (0.70%)	1 (0.50%)	1.00
Left atrium enlargement*	0	4 (2.10%)	0.145
P-axis*	0	1 (0.50%)	1.00
QRS axis			
Normal	119 (88.80%)	150 (79.80%)	
Right	14 (10.40%)	32 (17%)	0.089

Left	1 (0.70%)	6 (3.20%)	
T wave*	0	1 (0.50%)	1.00
Brugada Syndrome*	0	2 (1.10%)	0.513
U wave*	12 (9%)	31 (16.30%)	0.067
Intraventricular conduction delay*	7 (5.20%)	12 (6.30%)	0.680
Right Bundle Block*	0	4 (2.10%)	0.145

*Data were presented as mean ± standard deviation (minimum: maximum), median (IQR-Inter-quartile Range) or n (%). NA: Not Available (Statistical analysis could not be performed due to insufficient sample size). *: present.*

The distribution of the drugs used in the patient group is given in Table-3. Quetiapine was the most frequently used antipsychotic drug 45/176 (25.60%). There was no significant difference between antipsychotic drugs in terms of their proarrhythmic and ischemic effects on ECG (p> 0.05).

Table3. Distribution of the drugs used by the patients

Drug	n/n_{total} (%)
Quetiapine	45/176 (25.60%)
Olanzapine	37/176 (21%)
Risperidone	32/176 (18.20%)
Paliperidon	30/176 (17%)
Amisulpride	23/176 (13.10%)
Haloperidol	16/176 (9.10%)
Clozapine	16/176 (9.10%)
Aripiprazole	12/176 (6.80%)
Zuclopenthixol	11/176 (6.30%)
Chlorpromazine	5/176 (2.80%)

Independent risk factors considered to be specific for schizophrenia are given in Table-4. Schizophrenia has been identified as a risk factor for increased HR. When the value of the HR variable increased by 1 unit, the risk of schizophrenia increased 1.06 fold. The P-max variant was found to be a significant indicator for schizophrenia. As the value of the P-max variable increased by 1 unit, the probability of having schizophrenia increased 1.07 fold. The P-min variant was found to be a protective factor for schizophrenia and the probability of having schizophrenia was reduced by 13% when the value of the P-min variable increased by 1 unit. The fQRS was found to be another indicative factor for schizophrenia. In the presence of fQRS, the probability of having schizophrenia was 3.15 times higher than those without fQRS.

Table4. Independent risk factors considered to be effective in patients with schizophrenia

Risk Factor	B	OR (95%CI)	p-value
Heart Rate	0.06	1.06 (1.04:1.09)	<0.001
P-max	0.06	1.07 (1.04:1.09)	<0.001
P-min	-0.14	0.87 (0.83:0.91)	<0.001
QT dispersion	0.07	1.08 (1.04:1.11)	<0.001
Fragmented QRS			
present		Reference	
absent	1.15	3.15 (1.21:8.18)	0.019

The significance of final logistic regression model (p<0.001). OR: Odds ratio, CI: confidence interval

Discussion

In this retrospective study, ECG parameters of schizophrenic patients in psychiatric clinic were investigated in detail and compared with healthy controls. Proarrhythmic and ischemic ECG findings (HR, PWD, P-max, P-minus, P-dispersion, QT dispersion, fQRS, ST depression, Pathological Q) were detected significantly higher in schizophrenic patients compared to the healthy controls.

Life expectancy of schizophrenia patients has decreased by about 10 years. The most important diseases accused in the mortality of these patients are diabetes mellitus and cardiovascular diseases (19). Excessive weight gain due to the antipsychotic medications brings metabolic syndrome and other related medical problems to these patients (1, 4). Moreover, schizophrenia patients are unable to use health services properly for diagnosis, treatment and follow-up for other medical problems outside the psychiatric area due to low self-care and functional levels.

Although it is known that patients with schizophrenia have an increased risk of MI due to antipsychotic use, the underlying mechanisms have not been fully understood. While schizophrenic patients have cardiac symptoms, they usually have difficulties in applications to emergency departments (2). In a study of the ECG findings in schizophrenia patients, there was a sign of MI at 40 of 937 cases. However, in 30 of these 40 cases (75%), MI signs were not previously identified, and these cases were unrecognized or silent MI (2). In our study, pathological Q-wave was detected in 22 (11.60%) schizophrenia patient and in 2 (1.5%) subjects in the control group . While the cases in the control group were aware of MI, schizophrenic patients couldn't be aware of MI.

In the present study, patients with schizophrenia had significantly higher Pd, P-max duration and lower P-min duration compared to healthy controls. Changes leading to atrial remodeling such as elevated atrial pressure, atrial ionic remodeling, ischemia and metabolic stress may result in slowed conduction with inhomogeneous recovery, are substrates for AF development (20, 21). Pd indicates that a prolonged inhomogeneous and anisotropic distribution of connections between atrial fibers resulting in a discontinuous anisotropic propagation of sinus impulses with heterogeneous and discontinuous atrial conduction (22).

In a study examining 927,915 cases in Taiwan, patients with schizophrenia or bipolar disorder had a higher prevalence of AF than the general healthy population (23). Chronic CAD and acute myocardial infarction (AMI) are significant risk factors for AF evolution. In patients with CAD, left atrial overload owing to altered left ventricular relaxation caused by an ischemic zone, regional atrial fibrosis and slow conduction are associated with increased Pd (24, 25).

In the present study, patients with schizophrenia had positive fQRS more often as compared to the healthy controls (69/190–36.30% vs 10/133–7.50%, p = 0.001). fQRS is a relevant marker of conduction disturbance and by that parameter myocardial scar could be evaluated by ECG (26). fQRS was also a predictor of mortality and arrhythmic events in patients with various cardiac diseases, such as dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, acute coronary syndrome, Brugada syndrome, cardiac sarcoidosis, repaired tetralogy of Fallot and long-QT syndrome (27-29). Sudden cardiac death (SCD) has been found to be nearly three-times higher in schizophrenia patients, a finding driven by a several underlying mechanisms (30). Patients with schizophrenia show electrophysiological characteristics of the myocardial tissue, such as from stress, those lead to dysautonomia and activation of the hypothalamus–pituitary– adrenal axis, altering the autonomic tone and influencing circadian rhythms and ion channel variation, leading to CAD or causing drug induced cardiac fibrosis with certain antipsychotics used in the treatment of these common disorders (31, 32). Indeed, patients with schizophrenia are shown to have a higher prevalence of CAD than the general population (33). Reddy CV et al. (34) found that the combination of Q wave and fQRS showed high specificity (89%), sensitivity (91.4%), and negative predictable value (92.4%) for detection of scarred myocardium. In our study, the presence of pathologic Q-wave in the presence of myocardial infarction was found to be higher in patients with schizophrenia than control group (22/190–11.60% vs 2/134–1.50%, p < 0.001).Left ventricular hypertrophy and exaggerated accumulation of collagen occur in interstitial tissue, and give rise to non-ischemic myocardial fibrosis (34). In several studies, a strong association was detected between fQRS diagnosed on ECG and myocardial fibrosis, as assessed by gadolinium-enhanced cardiac magnetic resonance imaging (29).

Study Limitations

There are some limitations to be quoted. First of all, this was a cross-sectional study with a small sample size and there was no follow up for the patients to observe arrhythmic events. Also, Holter monitoring and electrophysiological evaluation couldn't be done due to cognitive dissonance of the schizophrenic subjects. Another limitation of the present study was that Pd and QTd parameters were measured manually, instead of by a computer-assisted program. One of the important limitations of the study was that our study group consisted only hospitalized patients. In hospitalized patients, co-morbidities can be seen more frequently due to other risk factors than their current psychiatric diseases. Further studies including non-hospitalized cases should be done to generalize our results. In the current study, the researchers were only concerned with the patients who used their drugs irregularly which restricts the evaluation of the possible relations between the drugs and the ECG changes. Lastly, in patients with pathologic Q-waves, the signs of previous MI were not confirmed by non-invasive imaging modalities such as echocardiography.

Conclusion

The current retrospective cross-sectional analysis of ECG findings indicated that patients with schizophrenia might have high prevalence of proarrhythmic and ischemic changes. P-wave dispersion, prolongation of QT-dispersion time and presence of fragmented-QRS, atrial fibrillation, ventricular fibrillation, and arrhythmia-related heart failure may partly explain the high frequency of premature deaths in such psychiatric disorder. During assessment of schizophrenia patients, psychiatrists should be aware of such ECG findings and should be in close contact with cardiologists to take relevant preventive steps.

Disclosure of conflict of interest

None of the author has any conflict of interest to disclose.

References

1. Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP. Medical comorbidity in schizophrenia. Schizophrenia bulletin. 1996;22(3):413-30.

2. Nielsen J, Juel J, Alzuhairi KS, Friis R, Graff C, Kanters JK, et al. Unrecognised myocardial infarction in patients with schizophrenia. Acta neuropsychiatrica. 2015;27(2):106-12.

3. Wu SI, Chen SC, Liu SI, Sun FJ, Juang JJ, Lee HC, et al. Relative Risk of Acute Myocardial Infarction in People with Schizophrenia and Bipolar Disorder: A Population-Based Cohort Study. PloS one. 2015;10(8):e0134763.

4. Kritharides L, Rye KA, Lambert TJ, Jessup W. Lipidology, cardiovascular risk, and schizophrenia. Current opinion in lipidology. 2016;27(3):305-7.

5. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. The Journal of clinical psychiatry. 2002;63(10):892-909.

6. Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. American heart journal. 1998;135(5 Pt 1):733-8.

7. Perkiomaki JS, Koistinen MJ, Yli-Mayry S, Huikuri HV. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. Journal of the American College of Cardiology. 1995;26(1):174-9.

8. Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. Heart rhythm. 2009;6(3 Suppl):S8-14.

9. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. Archives of general psychiatry. 2001;58(12):1161-7.

10. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. American heart journal. 2007;153(6):891-9.

11. Stimmel GL, Gutierrez MA, Lee V. Ziprasidone: an atypical antipsychotic drug for the treatment of schizophrenia. Clinical therapeutics. 2002;24(1):21-37.

12. Straus SM, Bleumink GS, Dieleman JP, van der Lei J, t Jong GW, Kingma JH, et al. Antipsychotics and

the risk of sudden cardiac death. Archives of internal medicine. 2004;164(12):1293-7.

13. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet (London, England). 2013;382(9896):951-62.

14. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart (British Cardiac Society). 2001;86(5):516-21.

15. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Jama. 2001;285(18):2370-5.

16. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. The American journal of medicine. 2002;113(5):359-64.

17. Liu Z, Hayano M, Hirata T, Quin Y, Tsukahara K, Ishimatsu T, et al. [Abnormalities of electrocardiographic P wave morphology and the relationship to electrophysiological parameters of the atrium in patients with idiopathic paroxysmal atrial fibrillation]. Journal of cardiology. 1998;32(3):189-96.

18. Das MK, Saha C, El Masry H, Peng J, Dandamudi G, Mahenthiran J, et al. Fragmented QRS on a 12-lead ECG: a predictor of mortality and cardiac events in patients with coronary artery disease. Heart rhythm. 2007;4(11):1385-92.

19. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA psychiatry. 2015;72(4):334-41.

20. Magnani JW, Williamson MA, Ellinor PT, Monahan KM, Benjamin EJ. P wave indices: current status and future directions in epidemiology, clinical, and research applications. Circulation Arrhythmia and electrophysiology. 2009;2(1):72-9.

21. Li D, Melnyk P, Feng J, Wang Z, Petrecca K, Shrier A, et al. Effects of experimental heart failure on atrial cellular and ionic electrophysiology. Circulation. 2000;101(22):2631-8.

22. Aytemir K, Ozer N, Atalar E, Sade E, Aksoyek S, Ovunc K, et al. P wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. Pacing and clinical electrophysiology : PACE. 2000;23(7):1109-12.

23. Yang HY, Huang JH, Lin YK, Hsu CY, Chen SA, Chen YJ. Bipolar Disorder and Schizophrenia Present Different Risks of Atrial fibrillation: A Nationwide Population-Based Analysis. Acta Cardiologica Sinica. 2014;30(1):46-52.

24. Elsasser A, Schlepper M, Klovekorn WP, Cai WJ, Zimmermann R, Muller KD, et al. Hibernating myocardium: an incomplete adaptation to ischemia. Circulation. 1997;96(9):2920-31.

25. Nielsen FE, Sorensen HT, Christensen JH, Ravn L, Rasmussen SE. Reduced occurrence of atrial fibrillation in acute myocardial infarction treated with streptokinase. European heart journal. 1991;12(10):1081-3.

26. Das MK, Suradi H, Maskoun W, Michael MA, Shen C, Peng J, et al. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. Circulation Arrhythmia and electrophysiology. 2008;1(4):258-68.

27. Das MK, Michael MA, Suradi H, Peng J, Sinha A, Shen C, et al. Usefulness of fragmented QRS on a 12-lead electrocardiogram in acute coronary syndrome for predicting mortality. The American journal of cardiology. 2009;104(12):1631-7.

28. Homsi M, Alsayed L, Safadi B, Mahenthiran J, Das MK. Fragmented QRS complexes on 12-lead ECG: a marker of cardiac sarcoidosis as detected by gadolinium cardiac magnetic resonance imaging. Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc. 2009;14(4):319-26.

29. Carey MG, Luisi AJ, Jr., Baldwa S, Al-Zaiti S, Veneziano MJ, deKemp RA, et al. The Selvester QRS Score is more accurate than Q waves and fragmented QRS complexes using the Mason-Likar configuration in estimating infarct volume in patients with ischemic cardiomyopathy. Journal of electrocardiology. 2010;43(4):318-25.

30. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. American heart journal. 2005;150(6):1115-21.

31. Rechlin T, Weis M, Spitzer A, Kaschka WP. Are affective disorders associated with alterations of heart rate variability? Journal of affective disorders. 1994;32(4):271-5.

32. Kelly DL, Wehring HJ, Linthicum J, Feldman S, McMahon RP, Love RC, et al. Cardiac-related findings at autopsy in people with severe mental illness treated with clozapine or risperidone. Schizophrenia research. 2009;107(2-3):134-8.

33. Ryan MC, Thakore JH. Physical consequences of schizophrenia and its treatment: the metabolic syndrome. Life sciences. 2002;71(3):239-57.

34. Querejeta R, Varo N, Lopez B, Larman M, Artinano E, Etayo JC, et al. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. Circulation. 2000;101(14):1729-35.