P-Wave and QT Dispersion in Pregnant Women with Preeclampsia

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ABSTRACT

Objective: Preeclampsia is an important cause of maternal and fetal mortality and morbidity worldwide. P-wave dispersion (P_d) and QT interval dispersion (QT_d) are direct measures of the nonhomogenity of atrial depolarization and ventricular repolarization, respectively, in electrocardiography (ECG). Recent studies have reported a significant role of prolonged P_d and QT_d in various cardiovascular diseases. Because the effect of acute pressure overload, which occurs in a preeclamptic setting, on the intra- and/or interatrial and ventricular conduction times remains unknown, we aimed to investigate the relation of P_d and QT_d with the presence and severity of preeclampsia.

Methods: Forty-eight consecutive pregnant women with preeclampsia and 55 healthy, age-matched pregnant women were included in this retrospective study between January and September 2015. The pregnant women with preeclampsia were divided into two groups according to disease severity as follows: mild and severe preeclampsia. A 12-lead ECG was performed for all the pregnant women before cesarean section operation.

Results: Compared with the healthy pregnant women, P_d and QT_d were significantly prolonged in patients with preeclampsia. Moreover, in the subgroups of preeclampsia, P_d was significantly increased in the severe group. P_d and QT_d were directly related to systolic and diastolic blood pressure, which are well-known validated indicators for the severity of preeclampsia.

Conclusion: Preeclampsia triggers an alteration of atrial depolarization and ventricular repolarization, which are evidenced by the prolongation of ECG parameters such as P_d and QT_d. ECG is a noninvasive, easy to use, and easily available diagnostic tool, which can be used in the assessment of atrial and ventricular electrical activity in pregnant women with preeclampsia.

Keywords: Preeclampsia, P-wave dispersion, QT dispersion, electrocardiography

INTRODUCTION

Preeclampsia, which is an important cause of maternal and fetal mortality and morbidity worldwide, is a pregnancy-associated multiorgan syndrome that affects approximately 6%–11% of all pregnancies. It is related to maternal [eclampsia; hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; abruption placentae and hemorrhage; pulmonary edema; and disseminated intravascular coagulation] and fetal (preterm delivery, perinatal death, intrauterine growth restriction, neurologic injury caused by hypoxia) complications (1, 2). Moreover, recent studies have reported an increased risk of long-term major adverse cardiovascular and cerebral events such as myocardial infarction, chronic hypertension, venous thromboembolism, and stroke in pregnant women with preeclampsia (3, 4). The mechanisms between preeclampsia and raised cardiovascular risk have not yet been elucidated.

Electrocardiographic (ECG) alterations in normal pregnancy, such as an increasing heart rate, reduction in PR interval, prolonged corrected QT interval (QTc), inverted or flattened T-waves, and leftward deviation of the QRS and T axes, have been reported in many previous studies (5, 6); however, only a few studies have evaluated the changes in ECG in hypertensive disorders of pregnancy in terms of P-wave morphology and the QT interval (7–10). P-wave dispersion (P_d), which is defined as the difference between the maximal and minimal P-wave durations recorded from many surface ECG leads, is an ECG marker related to a heterogenous and nonsustained distribution of the sinus impulse (11). Coronary artery disease, hypertension, obesity, and valvular heart disease have an impact on P_d values (12). A predictive role of P_d for prolonged interatrial and intra-atrial conduction times has been demonstrated in a previous study (13). In addition, elevated Pd values have been presented to be related to a raised risk of paroxysmal atrial fibrillation (11).

QT dispersion (QT_d) is defined as the difference between the maximum and minimum QT interval measured in many ECG leads (14). It is a direct indicator of the nonhomogenity of myocardial repolarization. A recent study has demonstrated an alteration related to ventricular repolarization, such as QT and

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QTc intervals, in pregnant women with preeclampsia (15). Furthermore, many studies have reported a clinical utility of QT_d as a prognostic factor for mortality in several diseases (16, 17).

Because the effect of acute pressure overload, which occurs in a preeclamptic setting, on the intra- and/or interatrial and ventricular conduction times remains unknown, we aimed to investigate the relation of P_d and QT_d with the presence and severity of preeclampsia. The correlations of P_d and QT_d with clinical and laboratory parameters were also determined.

METHODS

Forty-eight consecutive pregnant women with preeclampsia and 55 healthy, age-matched pregnant women, who underwent standard 12-lead ECG as a part of preoperative management for cesarean section operation between January and September 2015 at a tertiary educational and research hospital, were included in this retrospective study. The indications of cesarean section operation in healthy pregnant women were as follows: a history of previous uterine surgery, fetal distress, or malpresentation. The pregnant women with preeclampsia were divided into two groups according to disease severity as follows: mild and severe preeclampsia.

The diagnostic criteria of preeclampsia were as follows: after 20 weeks of gestation in a previously normotensive woman, a maternal systolic blood pressure of 140 mmHg or a diastolic blood pressure 90 mmHg measured at resting twice at 4-h intervals, and proteinuria as evidenced by either a measurement of 300 mg per 24-h urine collection or at least one positive dipstick reading. Severe preeclampsia was defined when the maternal blood pressure was 160/110 mmHg on two occasions at least 4 hours apart or one or more of the following conditions were present: increased liver transaminases to double the normal concentrations; acute renal failure; thrombocytopenia, cerebral, or visual symptoms; acute pulmonary edema; and severe right hypochondriac pain (18).

The exclusion criteria of the present study were as follows: a history of preeclampsia, preeclampsia superimposed on chronic hypertension, coronary artery disease, atrial flutter or fibrillation, atrioventricular conduction abnormality, kidney and liver disease, pulmonary disease, acute or chronic inflammatory diseases, hypo-hyperthyroidism, hyperlipidemia, diabetes mellitus, and ECGs without a clearly identifiable P-wave and QT interval.

Age, parity, gestational age at delivery, body mass index, smoking status, systolic and diastolic blood pressure, heart rate, proteinuria, creatinine, lipid profiles, hemoglobin, and platelet count were recorded from the hospital files of the study subjects. Verbal and written informed consent was taken from all the study participants. The study complied with the Declaration of Helsinki.

ECG Analysis

A standard 12-lead ECG was performed for all the study pregnant women before cesarean section operation. The 12-lead ECG was performed in a supine position following 10 minutes of rest at a paper speed of 50 mm/s and 1-mV/cm standardization. The P-wave duration was evaluated in twelve leads. The initial part of the P-wave was defined as the first atrial deflection from the isoelectric line, and the offset was the return of the atrial signal to baseline. The maximum (P_{max}) and minimum (P_{min}) P-wave durations were defined as the longest and shortest measurable P-wave durations, respectively, in any lead. P_d was calculated as the maximum minus minimum P-wave duration ($P_d=P_{max}-P_{min}$).

Heart rate (min), QRS complex duration (ms), RR interval (ms), QT interval (ms), and corrected QT interval (ms) according to Bazzet's formula (19) were calculated from the preoperative ECG. QT_d was obtained by calculating the difference between the maximum and the minimum QT interval measured in each ECG lead from the onset of QRS complex to the end of the T wave (20). The ECG parameters were compared between the preeclampsia and the control group, as well as between the "mild" and "severe" preeclampsia subgroups. The ECG findings were manually measured by a single senior noninvasive cardiologist who was unaware of the study. The ECG parameter measurements were performed with calipers in order to improve the accuracy and a magnifying lens was used to define the ECG deflection.

Statistical Analysis

Descriptive statistics were expressed as numbers (%) for categorical variables and as the mean ± standard deviation for numerical variables. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov) to determine if they were normally distributed. Differences between continuous and categorical variables among the groups were assessed using the unpaired Student's t-test and chi-square test. The Mann–Whitney U or Tukey test was performed to test the significance of pairwise differences for non-normal distributed data, using the Bonferroni correction to adjust for multiple comparisons. Pearson or Spearman correlation analysis was performed to determine the association of P_d and QT_d with the examined variables. An overall 5% type-I error level was used to infer statistical significance and a p-value less than 0.05 was considered significant. Statistical analyses were performed using the Statistical Package for Social Sciences version 20 (IBM SPSS Statistics for Windows, Armonk, NY, USA).

RESULTS

The present study included 48 pregnant women with preeclampsia (21 severe preeclampsia and 27 mild preeclampsia) (mean age, 27.0±4.6 and 27.9±5.7 years old, respectively) and 55 healthy pregnant subjects (mean age, 27.6±4.5 years old). The baseline demographic, clinical, and laboratory characteristics of the preeclampsia and control groups are summarized in Table 1. Systolic and diastolic blood pressures were significantly higher in the preeclampsia group than in the control group. However, gestational age at delivery, heart rate, and platelet

Table 1. Baseline demographic, clinical, and laboratory characteristics of the preeclampsia and control groups

	Preeclampsia (n=48)	Control (n=55)	p
Age (years)	27.5±5.2	27.6±4.5	0.924
Parity (number)			
- Nulliparous (%)	31 (64.58%)	34 (61.8%)	0.771
- Multiparous (%)	17 (35.42%)	21 (38.2%)	
Smoking (%)	10.42	12.73	0.721
BMI (kg/m²)	29.8±3.8	29.3±3.4	0.454
Gestational age at delivery (days)	257.5±19.1	270±19.9	0.002
Systolic blood pressure (mmHg)	155.4±16.2	108±8.9	<0.001
Diastolic blood pressure (mmHg)	100.6±10.9	70.2±9.3	<0.001
Heart rate (min)	82.4±9.5	86.7±11.5	0.04
Creatinine (mg/dL)	0.55±0.1	0.54±0.1	0.627
Total cholesterol (mg/dL)	204.68±40.1	217.26±37.2	0.102
High-density lipoprotein (mg/dL)	48.0±7.7	47.3±7.2	0.622
Low-density lipoprotein (mg/dL)	123.62±31.2	127.8±36.7	0.538
Triglyceride (mg/dL)	158.85±41.4	149.4±47.4	0.287
Hemoglobin (gr/dL)	11.6±1.3	11.5±1.3	0.620
Platelet (10^3/μL)	200604.2± 58747.8	228236.4± 65567.3	0.026

BMI: body mass index

Table 2. Baseline demographic, clinical, and laboratory characteristics in the severe and mild preeclampsia groups

	Severe preeclampsia (n=21)	Mild preeclampsia (n=27)	p
Age (years)	27.0±4.6	27.9±5.7	0.549
BMI (kg/m²)	30.2±4.0	29.6±3.7	0.567
Gestational age at delivery (days)	248.6±15.8	264.4±18.9	0.003
Proteinuria (mg/day)	4068±1713	688±282	<0.001
Systolic blood pressure (mmHg)	170±12	143±6	<0.001
Diastolic blood pressure (mmHg)	110±10	94±5	<0.001
Heart rate (min)	84±10	81±9	0.441
Creatinine (mg/dL)	0.57±0.11	0.53±0.08	0.184
Total cholesterol (mg/dL)	198.24±32.47	208.5±38.43	0.331
High-density lipoprotein (mg/dL)	48.2±7.3	47.9±8.2	0.865
Low-density lipoprotein (mg/dL)	126.84±32.4	118.64±27.8	0.351
Triglyceride (mg/dL)	159.1±43.4	157.2±39.8	0.875
Hemoglobin (gr/dL)	11.6±1.6	11.7±1.1	0.849
Platelet (10^3/μL)	201380±56519	200000±61487	0.937

BMI: body mass index

Table 3. Comparison of the ECG parameters between the preeclamptic and healthy pregnant women

	Preeclampsia (n=48)	Control (n=55)	p
P_{max} (ms)	96.7±6	93.2±9.9	0.032
P_{min} (ms)	35.6±6.8	41.8±8.9	<0.000
P_d (ms)	56.8±8.8	47.6±8.1	<0.000
QT (ms)	395±19.9	374.7±18.3	<0.000
QT_c (ms)	442.8±17.9	433.4±21.4	0.017
QT_d (ms)	25.7±5	21.6±1.0	<0.000

P_d: P-wave dispersion; QT_c: corrected QT; QT_d: QT dispersion

counts were found to be lower in the pregnant women with preeclampsia than in the control subjects. When we compared the baseline demographic, clinical, and laboratory characteristics in the severe and the mild preeclampsia groups (Table 2); systolic and diastolic blood pressure and proteinuria were significantly higher in the severe group than in the mild preeclamptic group. However, as expected, the gestational age at delivery was significantly lower in the severe group than in the mild preeclamptic pregnant group.

When the ECG parameters were evaluated between the preeclampsia and control groups (Table 3), the parameters of both the P-wave (P_{max}, P_{min}, and P_d) and QT interval (QT, QT_c, and QT_d) durations were significantly different between the two groups, whereby all the parameters were found to be higher in the preeclampsia group than in the control group, except P_{min}, which was lower in the individuals with preeclampsia. Moreover, when these parameters were compared in the subgroups of preeclampsia (Table 4), only the parameters of the P-wave duration (P_{max}, P_{min}, and P_d) were significantly different, whereby P_{max} and P_d were increased and P_{min} was decreased in the severe preeclampsia group. There was no difference between two groups in terms of QT, QT_c, and QT_d.

The correlations of both P_d and QT_d with the clinical and laboratory parameters in the pregnant women with preeclampsia

Table 4. Comparison of the ECG parameters between the severe and mild preeclampsia groups

	Severe preeclampsia (n=21)	Mild preeclampsia (n=27)	p
P_{max} (ms)	99.2±7.1	94.7±4.3	0.015
P_{min} (ms)	33.3±5.7	37.4±7.1	0.036
P_d (ms)	59.6±9.6	54.4±7.2	0.030
QT (ms)	397.4±21.9	393.2±18.4	0.466
QT_c (ms)	444.0±18.9	441.8±17.6	0.669
QT_d (ms)	25.7±5.3	25.6±5.1	0.995

P_d: P-wave dispersion; QT_c: corrected QT; QT_d: QT dispersion

Table 5. Correlation analysis between P_d and clinical and laboratory parameters

	r	p
Gestational age at delivery	−0.129	0.193
Systolic blood pressure	0.480	<0.001
Diastolic blood pressure	0.414	<0.001
Proteinuria	0.116	0.434
P_{max}	0.148	0.135
P_{min}	−0.249	0.011
QT	0.174	0.079
QT_c	0.181	0.068
QT_d	0.242	0.014

P_d: P-wave dispersion; QT_c: corrected QT; QT_d: QT dispersion

Table 6. Correlation analysis between OT_d and the clinical and laboratory parameters

	r	p
Gestational age at delivery	−0.196	0.048
Systolic blood pressure	0.496	<0.001
Diastolic blood pressure	0.464	<0.001
Proteinuria	−0.154	0.294
P_{max}	0.120	0.227
P_{min}	−0.116	0.242
P_d	0.242	0.014
QT	0.228	0.021
QT_c	0.115	0.246

P_d: P-wave dispersion; QT_c: corrected QT; QT_d: QT dispersion

are presented in Tables 5 and 6. P_d was positively correlated with the systolic (r=0.480, p<0.001) and diastolic blood pressure (r=0.414, p<0.001) and QT_d (r=0.242, p=0.014). In addition, QT_d was directly related to both the systolic (r=0.496, p<0.001) and diastolic blood pressure (r=0.464, p<0.001); however, it was inversely correlated with gestational age at delivery (r=-0.196, p<0.048).

DISCUSSION

The present study is the first to report significant relations between both P_d and QT_d and the presence of preeclampsia in pregnant women at the same time. It was found that P_d and QT_d were significantly prolonged in patients with preeclampsia than in healthy pregnant women in this study. Furthermore, these parameters were directly related to systolic and diastolic blood pressure, which are well-known validated indicators for the severity of preeclampsia.

Preeclampsia is one of the important cardiovascular risk factors. The main pathophysiological mechanisms of this setting are endothelial dysfunction, severe inflammation, hypercoagulability, increased oxidative stress, and decreased uteroplasental blood flow (21, 22). A recent study reported that the 10-year cardiovascular disease risk according to the Framingham score is 31% higher with a past history of preeclampsia and 27% higher with gestational hypertension (21). Also, the coronary artery calcium score was found to be raised in patients with a history of preeclampsia after adjusting for cardiovascular risk factors, in the Rochester Family Heart Study (23). Although many previous studies present findings and hypotheses about preeclampsia, the main causal association between preeclampsia and cardiovascular disease has not been precisely elucidated. In our study, in pregnant women with preeclampsia, well-known cardiovascular disease risk factors, such as systolic and diastolic blood pressure, were found to be higher than those in the healthy pregnant women, concordant with previous studies. Moreover, these parameters increased as the severity of preeclampsia increased.

P_d, which reflects the size of the atria and is reported to be affected by various cardiovascular risk factors, has also been reported to be independently related with an elevated risk of atrial fibrillation (AF), recurrent transient ischemic attacks, and stroke (24). Abnormal changes in P-wave morphology during pregnancy have been demonstrated as a potential predictor of hypertensive disorders in previous studies (7, 25). P-wave duration, including P_d, was reported to be significantly increased in the pregnant women with preeclampsia than in the healthy pregnant women in the study of Raffaelli et al. (10). There are many recent studies investigating the role of P_d in various cardiovascular diseases, such as hypertension (26), acute ischemic stroke (27), coronary artery disease following coronary artery bypass surgery (28), myocardial ischemia (29), Valsalva maneuver (30), renal dysfunction (31), and stable angina pectoris (32). In addition, Dilaveris et al. (33) reported increased P_{max} and P_d as novel risk predictors for paroxysmal AF in patients without cardiac disease. P_d was demonstrated to be significantly prolonged in hypertensive subjects without any relation with blood

pressure, left atrial dimensions, or a left ventricular mass, and was found to be an independent predictor for the onset of AF in a recent prospective study (34). In our study, P_d and P_{max} were found to be increased in the preeclampsia group than in the control group and were also associated with disease severity. In addition, we demonstrated a significant relation between P_d and the systolic and diastolic blood pressure, different from the study by Ciaroni et al. (34). Kirbas et al. (35) presented that P_{min} and P_d were significantly changed in pregnant women with preeclampsia compared with healthy pregnant women. Concordant with Kirbas et al.'s (35) study, P_d values were significantly prolonged, related to disease severity, in the pregnant women with preeclampsia than in the healthy pregnant women in our study. Our study novelty was to report significant associations between both the P-wave and QT interval duration parameters, as indicated by P_d and QT_d, and the presence and severity of preeclampsia at the same time. The discriminative effect of P_d for mild and severe preeclampsia may be beneficial in clinical practice. Although a potential pathophysiological linkage between the left atrial structural and functional abnormality and the development of hypertensive disorders remains elusive, an abnormal expansion of the blood volume, high or high-normal blood pressure, and a raised sensitivity to the vasopressor effect of the renin-angiotensin system may play roles for the development of this setting (5, 7).

The clinical utility of the QT_d as a predictor of cardiovascular mortality has been reported in various cardiovascular diseases, such as hypertension, chronic renal failure undergoing dialysis, type 2 diabetes, acute ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, metabolic syndrome, and obstructive sleep apnea syndrome, in previous studies (36-41). Preeclampsia and other states that lead to abnormal uterine perfusion may change the ventricular repolarization before clinical symptoms occur (15). Raffaelli et al. (10) reported significant changes of the ventricular repolarization in pregnancies complicated by preeclampsia. Women with preeclampsia demonstrated a lower HR, a prolonged QTc interval, and a higher QT_d than the control group. Moreover, Isezuo and Ekele (9) presented an important relation between eclampsia and prolonged ventricular repolarization, where heart rate and QTc were found to be higher in women with preeclampsia than in healthy pregnant women (9). Our study findings supported the study findings of Raffaelli et al. (10) However, we did not observe any relation between the QT interval duration including QT_d and the severity of preeclampsia in our study. Moreover, our study findings are in contrast to the study findings of Isezuo et al. (9) in terms of heart rate. In the light of recent study findings, it is worth mentioning that QT_d is an important independent indicator for the heterogenity of ventricular repolarization and its prolongation is related with an elevated incidence of life-threatening ventricular arrhythmias, which is a trigger factor for all-cause mortality.

Endothelial dysfunction, severe inflammation, increased oxidative stress, and decreased uteroplasental blood flow, which are seen in preeclampsia, may play roles in the development of alternance of atrial depolarization and ventricular repolarization. Further large clinical studies with more study subjects are needed to elucidate the precise link between the P-wave and QT interval duration parameters, especially P_d and QT_d, with the presence and severity of preeclampsia.

Study Limitations

The present study has some limitations. First, this study had a non-randomized and retrospective design based around data from a single center; therefore, the study was subject to selection bias. Second, the study population was relatively small; however, we were still able to demonstrate an important relationship between P_d and QT_d and the presence of preeclampsia. Third, we manually calculated the P-wave and QT interval duration parameters using a magnifying lens instead of using a computer-assisted software program in the absence of Holter monitoring and electrophysiological evaluation, which likely led to increased inter- and intraobserver variability. Finally, P_d and QT_d may be influenced by the autonomous nervous system, psychological state, and time of day, which were not assessed in our study (42, 43).

CONCLUSION

We demonstrated a significant relation between both prolonged P_d and QT_d and the presence of preeclampsia in pregnant women. Preeclampsia triggers an alteration of atrial depolarization and ventricular repolarization, which are evidenced by prolongation of the ECG parameters such as P_d and QT_d. Electrocardiography is a noninvasive, easy to use, and easily available diagnostic tool, which can be used in the assessment of atrial and ventricular electrical activity in pregnant women with preeclampsia.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

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