Cardiac Autonomic Balance is Impaired in Preeclampsia

Kardiyak Otonomik Denge Preeklampside Bozulmaktadır

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ABSTRACT Objective: Preeclampsia is characterized by marked increase in peripheral vascular resistance resulting in high arterial blood pressure and proteinuria in pregnancy. Autonomic imbalance may play a role in the pathogenesis of preeclampsia. Our aim was to investigate the cardiac autonomic status in preeclampsia by using heart rate variability (HRV). **Material and Methods:** Age- and gestational age-matched subjects consisting of 34 pregnant women with preeclampsia and 29 healthy pregnant women were enrolled in the study. In order to rule out the effect of any medication and concomitant disease all participants were selected among those without any medication at that time and underwent a detailed physical examination and blood chemistry analysis. Analysis of HRV was performed in all subjects from 24-hr Holter recording data. Preeclampsia was defined as diastolic blood pressure over 90 mmHg in previously normotensive woman, and proteinuria over 300 mg/day. **Results:** In preeclamptic pregnant women, the HRV indices that reflect both parasympathetic activity and global autonomic functions were lower than in healthy pregnants. **Conclusion:** Although it was speculated that low circulating volume causes direct baroreflex-mediated stimulation of the sympathetic system resulting with high vascular resistance in preeclamptic patients, our results imply that alteration in central regulation mechanisms may have a role in autonomic imbalance in preeclamptic women.

Key Words: Pre-eclampsia; autonomic nervous system diseases

ÖZET Amaç: Preeklampsi, gebelikte periferik damar direncinin aşırı artışı sonucunda yüksek arteriyel kan basıncı ve proteinüri ile karakterizedir. Preeklampsinin patogenezinde otonomik dengesizlik rol oynayabilir. Bu çalışmada kalp hızı değişkenliği (KHD) analizini kullanarak preeklampside kardiyak otonomik durumu değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Yaş ve gebelik yaşı denk olan 34 preeklamptik gebe ve 29 sağlıklı gebe çalışmaya alındı. Herhangi bir tedavi ve eşlik eden hastalığın etkisini ortadan kaldırabilmek için çalışmaya alınan tüm bireyler çalışma sırasında herhangi bir ilaç kullanmayan olgulardan seçildi ve tüm bireylerde detaylı bir fizik muayene ve kan kimyası analizi yapıldı. KHD analizi tüm olgularda 24 saatlik Holter kayıtlarındaki verilerden yararlanılarak yapıldı. Preeklampsi, daha önce kan basıncı normal olduğu halde, diyastolik kan basıncının 90 mmHg düzeyinin üzerinde olması ve 300 mg/gün düzeyinin üzerinde proteinüri bulunması olarak tanımlandı. **Bulgular:** Preeklamptik gebelerde KHD'nin hem parasempatik aktiviteyi hem de global otonomik fonksiyonları yansıtan belirteçleri sağlıklı gebelerdekinden daha düşüktü. **Sonuç:** Preeklamptik hastalarda düşük dolaşım hacminin doğrudan barorefleks uyarı ile sempatik sistemi uyardığı ve sonuçta yüksek damar direncine neden olduğu yönünde tahminlerde bulunulmuşsa da, çalışmamızın sonuçları, preeklamptik kadınlarda santral regülasyon mekanizmalarındaki değişikliklerin otonomik dengesizlikte rolü olduğunu düşündürmektedir.

Anahtar Kelimeler: Preeklampsi; otonomik sinir sistemi bozuklukları

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Preeclampsia is the leading cause of maternal and neonatal death during pregnancy. It is characterized by a marked increase in peripheral vascular resistance resulting in high arterial blood pressure and proteinuria. Although the pathophysiologic basis of preeclampsia is not well established and plasma cathecolamine levels have been the main subject of related studies, the data are conflicting.[1-4] In preeclampsia the activity of the autonomic nervous system is disturbed, possibly due to alterations in central control mechanisms or impairment of afferent sensitivity.[5,6]

HRV, the degree of fluctuation of the beat-to-beat differences in cardiac rhythm, was shown to be a reliable, non-invasive marker of autonomic nervous system activity. Recent advances in technology have enabled more accurate and precise information via high quality recordings and the automated analysis of 24-hour ECG.[7]

Since the analysis of HRV was introduced in 1981, the quantitative evaluation of beat-to-beat cardiovascular control has brought new insights into the assessment of the autonomic nervous system function in health and disease.[8] A decrease in HRV was reported to predict coronary heart disease morbidity and mortality in apparently healthy populations and in patients after an acute coronary event.[8] Although there has been a growing interest in HRV research in various disease states, such as diabetic neuropathy, anemia due to vitamin B_{12} and iron deficiency, acute leukaemias, allergic rhinitis, and primary nocturnal enuresis, its influence on clinical decisions is still limited.[9-14] The exceptions are the risk assessment of patients after myocardial infarction and early diagnosis of diabetic autonomic neuropathy.[7] Despite these reports, the physiologic mechanisms of HRV are still debated. Thus, the changes in HRV can not be predicted most of the time, and individual research is needed in various clinical situations.

We hypothesized that autonomic imbalance in preeclampsia might be responsible for the increased peripheral vascular resistance. Accordingly, we designed the present cross-sectional, controlled study in order to evaluate the autonomic status of preeclamptic women by using time domain analysis of heart rate variability.

MATERIAL AND METHODS

A consecutive group of 34 (with a mean age of 29 ± 4 years) pregnant women with preeclampsia, and without twin pregnancy, intra-uterine growth retardation or heamolysis, elevated liver enzymes, low platelet count (HELLP) syndrome were enrolled in the study. The control group was composed of 29 consecutive age- and gestational age-matched normal pregnant women (with a mean age of 27 ± 4 years) in the third trimester of their pregnancies. All participants were free of any concomitant systemic or cardiac disease. A detailed history, physical examination, routine blood chemistry, electrocardiography and echocardiography were considered satisfactory for excluding any other concomitant disease. The study was reviewed and approved by the institutional Ethics Committee of Gulhane Military Medical School and all participants signed the written informed consent.

Preeclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy.[15] These require two recordings of blood pressure of >140/90 mmHg at least four hours apart in previously normotensive women and proteinuria ≥ 300 mg/day, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available.

Twenty-four-hour ambulatory electrocardiographic recordings were obtained from each subject with a digital Holter recorder (Rozinn Electronics, Inc., Glendale, NY, USA). In preeclamptic patients, all of whom were hospitalized, Holter recording was performed immediately upon diagnosis. Therefore, we could obtain Holter data before preeclampsia therapy, which otherwise might affect the results. Moreover, control group subjects were instructed not to make any extraordinary changes in the normal course of their daily lives. This was also confirmed during the removal of the device. Holter recordings were interpreted by an experienced cardiologist who was blinded to the status of

the participants. Due to technical limitations of the analysis software, only the following time-domain indices of HRV from a 24-hour recording were calculated and evaluated: standard deviation of normal R-R intervals (SDNN), standard deviation of successive differences in normal cycles (SDANN), root mean square of successive differences between normal sinus R-R intervals (RMSSD), number of R-R intervals exceeding 50 ms (SNN50), percentage difference between adjacent normal R-R intervals exceeding 50 ms (PNN50) and HRV triangular index.[16] Among them, RMSSD, SNN50 and PNN50 primarily reflect parasympathetically mediated changes in heart rate. The remaining time-domain variables reflect a mixture of parasympathetic, sympathetic and other physiologic influences. In addition to HRV variables, basic rhythm and associated problems such as atrial or ventricular arrhythmias were carefully evaluated.

Continuous and categorical variables were expressed as mean ± 1 standard deviation and percentages, respectively. In comparison of the variables Student's t test and Mann-Whitney U test were used according to the normality test results, which were tested by Kolmogrow–Smirnow test. A chi-square test was also used for categorical data comparison. A p value below 0.05 was considered significant.

RESULTS

There were no statistically significant differences between the study group and the control group in relation to age, body mass index, hemoglobin and hematocrit levels, AST, platelet count, gestational age and number of pregnancies. Although within normal range in all participants, only ALT was significantly higher in preeclamptic group ($p< 0.05$). Demographic and clinical characteristics of study subjects were listed in Table 1. All subjects were in sinus rhythm without episodes of sustained atrial or ventricular arrhythmias.

The statistical comparisons between the groups were shown in Table 2. The RMSSD was not significantly different between groups ($p> 0.05$).

TABLE 1: Demographic and clinical characteristics of patients.

Characteristics	Preeclamptic women (n= 34)	Normal pregnancy (n= 29)	p
Mean age	29±4	27 ± 4	0.169
Number of pregnancies			
0	10 (29%)	8 (28%)	
1	19 (56%)	16 (55%)	0.799
2	5 (15%)	5 (17%)	
Gestational age at the time of diagnosis and examination for controls (week)	29.2 ± 3.8	30.1 ± 3.6	0.213
Gestational age at delivery (week)	33 ± 3	39 ± 6	<0.05
Delivery			
Caesarean section	23 (67%)	3 (10%)	
Normal delivery	5 (15%)	26 (90%)	<0.05
Stillbirth	6 (18%)	0	
Body mass index	28.7 ± 4.1	28.1 ± 3.9	0.061
Hemoglobin (mg/dL)	12.4 ± 2.1	12.6 ± 2.2	0.612
Hematocrit (%)	37.6 ± 6.5	38.1 ± 6.9	0.598
Systolic BP	144 ± 18	108 ± 20	<0.05
Diastolic BP	95 ± 10	78 ± 9	<0.05
ALT (IU)	15.6 ± 4.9	14.9 ± 7.7	<0.01
AST (IU)	17.3 ± 5.5	20.2 ± 6.4	0.074
Platelet count ($10^3/mm^3$)	222 ± 75	244 ± 69	0.210

BP: Blood pressure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; body mass index, ALT, AST, platelet count, hemoglobin and hematocrit values were the values at the time of the study.

TABLE 2: Statistical comparison of HRV variables.

	Preeclamptic Women	Normal Pregnancy	p
SDNN	109 ± 52 (51-160 [110])	130 ± 56 (62-153 [127])	<0.05
SDANN	80 ± 33 (40-110 [82])	108 ± 37 (45-140 [106])	<0.05
RMSSD	46 ± 59 (24-135 [51])	34 ± 19 (20-82 [35])	=0.267
HRV-Triangular Index	27 ± 9 (15-36 [28])	32 ± 10 (21-45 [34])	<0.05
SNN50 Count	6301 ± 7673 (1220-18341 [6972])	14357 ± 7308 (8392-20506 [13978])	<0.05
PNN50	29 ± 10 (17-41 [28])	23 ± 9 (12-35 [21])	<0.05

Values in parentheses are maximum and minimum, and values in brackets are the median of the data. Values expressed as mean ± 1 standard deviation.
(SDNN), the standard deviation of all normal sinus R-R intervals over 24 hours; (SDANN), the standard deviation of all averaged normal sinus R-R intervals for each 5-minute segment in the 24-hour recordings; (RMSSD), root mean square of successive differences between normal sinus R-R intervals; (HRV triangular index), the ratio of the number of all R-R intervals to the height of the histogram created by the charting of all the RR intervals; (SNN50 count), number of R-R intervals exceeding 50 ms; (PNN50), the percentage of difference between adjacent normal R-R intervals that are greater than 50 ms computed over the entire 24-hour ECG recording.

However, the SDNN, SDANN, HRV triangular index and SNN50 count values were significantly lower in preeclamptic group than in normal pregnant women ($p< 0.05$) and the PNN50 value was significantly higher in preeclamptic women than in normal cases ($p< 0.05$).

DISCUSSION

This study showed that HRV parameters were decreased in patients with preeclampsia. Our results implied sympathetic predominance in women with preeclampsia, because we determined a decrease in HRV indices reflecting both global and parasympathetic withdrawal. This finding is consistent with the hypothesis that sympathetic activation is present in preeclamptic pregnancies.

Among the time-domain indices of HRV, RMSSD, SNN50 and PNN50 primarily reflect parasympathetically mediated changes in heart rate.[16] Though preeclamptic patients had depressed levels, we found lower values for these indices in the preeclamptic group except for RMSSD. The lack of difference for RMSSD may be explained only by chance but our findings implied sympathetic dominance during pregnancy in line with previous studies performed by spectral analysis of HRV and cold pressor test in preeclampsia.[17,18] The sympathetic response in preeclampsia may account for low circulating volume and high vascular resistance.[19,20] Plasma volume constriction was suggested to induce direct baroreflex-mediated stimulation of the sympathetic system.[21-23] However, Metsaars et al found no evidence to suggest that therapeutic plasma volume expansion had any effect on sympathetic activity might constitute the primary process rather than a constricted plasma volume.[24] Similarly, Courtar et al showed that a subnormal plasma volume coincided with a higher sympathetic activity and lower baroreflex sensitivity in normotensive formerly preeclamptic women.[25] Indeed, Rang et al reported sympathetic overactivity in pregnant women in whom preeclampsia subsequently developed compared with women who had a normal pregnancy.[26] Moreover, there are numerous studies declaring the sympathetic overactivity in preeclampsia but none of these studies used time-domain analysis of HRV.[5,27-29] In view of our findings, we suggest that a central autonomic imbalance may play a role in preeclampsia.

STUDY LIMITATIONS

We used only the time-domain parameters of HRV for technical reasons. The study would have yielded better results if frequency-domain parameters could have been included. However, we think the study is still valuable because time-domain and frequency-domain parameters are related to each other. A change in one of them is generally suggestive of a change in the other.[30] In addition, the time-domain indices of HRV are more useful in indicating vagal activity.[31]

We also could not evaluate the blood pressure variability for technical reasons; however, blood pressure variability was reported to influence HRV, and the correlation between blood pressure variability and HRV was very good in preeclamptic women.[32,33]

Another point is the activity of the subjects. The study group was hospitalized and was confined to bed rest, but the control group consisted of ambulatory pregnant women. Parasympathetic activity is expected to be higher in patients restricted to bed and hence, the sympathetic overactivity in our study may be lower than the expected values.

In conclusion, the HRV is decreased in preeclampsic pregnancy. This result has two implications: 1- Parasympathetic withdrawal exists in preeclamptic women; 2- There may be an increased risk of ventricular arrhythmias in this patient group; however, this issue remains to be clarified in large-scale prospective trials. Future studies will clarify the exact mechanism of the decreased HRV.

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