Maternal respiratory sinus arrhythmia captures the severity of pre-eclampsia

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Abstract

Pre-eclamsia is a gestational disease that leads to hemodynamic disorders, hypoperfusion of end organ and multiple organ failure. Respiratory sinus arrhythmia is known to be participated in regulation of heart rate, cardiac output, blood pressure and peripheral vascular tone. The study was aimed to the survey of respiratory sinus arrhythmia involvement in the maternal cardiovascular system regulation in PE. 116 patients at 28-38 weeks of gestation were enrolled in the study. 30 women with healthy pregnancy were included in Group I (control). In Group II, 49 pregnant women with mild-moderate pre-eclampsia were observed. 37 patients with severe pre-eclampsia were monitored in Group III. The types of maternal central hemodynamics and maternal heart rate variability were investigated. The decreased autonomic tone was found in pre-eclamptic patients. The increased sympathetic activity in the mild-moderate pre-eclampsia could contribute to better perfusion of end organ. The explored autonomic modulations were associated with gradual decrease of respiratory sinus arrhythmia. Severe pre-eclampsia was featured by dramatic sympathetic overactivity. High peripheral vascular resistance and hypovolemia caused hypoperfusion of end organ in severe pre-eclamptic patients. Therefore, the decreased respiratory sinus arrhythmia was a sign of cardiac failure. Maternal respiratory sinus arrhythmia was an evident biophysical marker of pre-eclampsia and could be used as an additional criterion of its severity.

Key words: pre-eclampsia, heart rate variability, respiratory sinus arrhythmia

Pre-eclampsia (PE) is a main reason of adverse maternal and perinatal outcomes. PE occurs during pregnancy only in humans. Placental ischemic syndrome is an initial event in multiple-role scenario of PE [3, 6, 8]. The increased synthesis of the pro-inflammatory substances induce endothelial dysfunction, oxidative stress and thrombophilia. The release of vasoconstrictors may cause fluid redistribution and hypertension. PE destroys gestational autonomic resetting based on increased vagal tone those provides hypervolemia and systemic vasodilation in healthy pregnancy [1, 7, 10]. Hypovolemia and general vasoconstriction are the features of hemodynamics in PE.

The well-known sympathetic overactivity modulates the autonomic response by suppression of vagal regulation [6, 10]. Maternal sympathetic tone is associated with gestational age and heart rate in PE. The relationship with such parameters as: maternal age, hemoglobin and body mass index (BMI) was not confirmed [7]. The lack of parasympathetic regulation is known as a typical autonomic disorder in pre-eclamptic patients. This peculiarity is associated with decreased diaphragmatic motility due to abnormally elevated intraabdominal pressure [4].

Respiratory sinus arrhythmia (RSA) captures parasympathetic impact on cardiovascular system. RSA is known to be involved in regulation of heart rate, cardiac output, blood pressure and peripheral vascular tone of end organ [1]. The decreased RSA is a sign of the cardiac failure [10]. Heart rate variability (HRV) is a convenient instrument of the autonomic nervous system investigations. The root mean square of successive heartbeat interval differences (RMSSD) is considered as a RSA-related parameter [6, 7].

The study was aimed to the survey of RSA involvement in the maternal cardiovascular system regulation in PE.

Materials and methods

The study protocol was approved by the Bioethics Committee of Kharkiv Medical Academy of Postgraduate Education. The eligible participants were informed about the study's methodology, its aims, objectives, indications and eventual complications before enrollment. Patients from the department of maternal-fetal medicine were selected randomly. All the patients who met the inclusion criteria gave written informed consent to participate [2]. The inclusion criteria: diagnosed PE based on the blood pressure higher than 140/90 mm Hg in two separate occasions 6 hours apart, a positive proteinuria test in two mild-stream urine samples collected 4 hours apart. The exclusion criteria: multiple pregnancy, eclam-

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psia, pre-existing medical disorders like diabetes mellitus, metabolic syndrome, cardiac diseases, renal disease, thyrotoxycosis and chronic hypertension. If blood pressure was 140 to 159 mm Hg systolic and 90 to 109 mm Hg the patient was included in mild-moderate PE Group. Severe PE was diagnosed in case of blood pressure was higher 160 mm Hg systolic and 110 mm Hg diastolic or (and) thrombocytopenia, serum creatinine more than 1.1 mg/l, elevated blood concentration of liver transaminases, pulmonary oedema, cerebral or visual disturbances. The patients who had no gestational complications and medical disorders including chronic infections and tobacco smoking were enrolled in Group I. All patients included in the study were inhabitants of Eastern Ukraine. The study was conducted from January 2014 to December 2015.

116 patients at 28-38 weeks of gestation were enrolled. 30 women of healthy pregnancy and were included in Group I (control). In Group II, 49 pregnant women with mild-moderate PE were observed. 37 patients with severe PE were monitored in Group III.

All examined pre-eclamptic patients received antihypertensive drugs. The choice of antihypertensive agent was made according to the type of central maternal hemodynamics (CMH) determined by bio-impedance cardiography. It was estimated the values of cardiac index (CI) and total peripheral vascular resistance (TPVR). The hyperkinetic type of CMH was associated with high CI and low TPVR. The pre-eclamptic women with eukinetic type of CMH had high or normal CI and increased TPVR, and the pre-eclamptic patients with low CI and high TPVR had the hypokinetic type of CMH [9]. The pregnant women with hyperkinetic type of CMH took carvedilol 6.25-12.5 mg 2 times daily, in case of the eukinetic type – methyldopa 250-500 mg 4 times daily and in cases of the hypokinetic one – methyldopa 500 mg 4 times daily combined with nifedipine 20 mg 2 times daily.

The maternal ECG tracing was recorded with the application of "Cardiolab" software (Scientific Research Center "KhAI-Medica", Ukraine). Further processing for HRV temporal and spectral transforming was performed. The recordings lasted for 10 minutes in the horizontal maternal position on her right side. The values of total power (TP) and its spectral compounds, i.e. the very low frequency (VLF), the low frequency (LF), the high frequency (HF) and LF/HF ratio or sympatho-vagal balance, were determined. The temporal characteristics of the fetal HRV: the standard deviation of normal to normal intervals (SDNN), RMSSD, the proportion of the number of pairs of NNs differing by more than 50 ms divided by the total number of NNs (pNN50), the amplitude of mode (the most frequent value of NN interval or the highest column in the histogram) – the number of NN intervals included in the pocket corresponding to the mode measured in percentages (%) (AMo) and the stress index – SI = AMo(%)/(2×Mo×Var); Var = $NN_{max} - NN_{min}$; (SI) were calculated.

The results thus obtained were analyzed with an ANOVA test to compare data between groups. The significance was set at p-value < 0.05. For the statistical analysis of relationship between X and Y, the correlations coefficients were estimated with Spearman's test. Microsoft Office 2010 Excel software was used for statistical analysis.

Results

The mean age values were 26.9 ± 5.2; 25.4 ± 8.0 and 25.9 ± 7.5 years in Group I, Group II and Group III respectively. The mean values of the gestational age were 37.2 ± 2.6; 35.6 ± 2.9 and 31.4 ± 3.1 weeks in Group I, Group II and Group III respectively ($p < 0.05$, the differences were statistically significant compared to Group I). Therefore, the patients in Group II had the late-onset PE and the early-onset PE was determined mostly in Group III. The BMI values in the same groups were 24.9 ± 5.2; 28.3 ± 7.0 and 29.4 ± 8.3 ($p < 0.05$, the differences were statistically significant compared to Group I). BMI in PE was found significantly higher than in healthy pregnancy Group I.

The study of CMH types worked out elevated both CI and TPVR mean values in mild-moderate PE Group (table 1). The values of TPVR demonstrated a considerable growth in severe PE. CI was significantly decreased in Group III. The hyperkinetic type of CMH was found in 77.6% and the eukinetic one was determined in 22.4% of pre-eclamptic patients in Group II. The hypokinetic type of CMH was revealed in 56.8% of women in Group III and 43.2% of severe pre-eclamptic patients were found to have an eukinetic pattern of CMH. The hyperdynamic circulation was typical for mild-moderate PE and hypodynamic one was found in severe PE. The centralization of blood circulation was determined in Group III.

The decreased autonomic tone was found in pre-eclamptic patients (table 2). As horizontal position on the right side was associated with additional aortocaval compression the abnormal increase of sympathetic regulation was revealed.

Table 1. The parameters of bioimpedance cardiography in the study population

Index, units of measure	Group I	Group II	Group III
CI, L/min/m^2	3.6 ± 0.8	3.9 ± 1.4*	2.2 ± 1.0*/†
TPVR, dyn·s/cm^5	1214.5 ± 128.2	1372.8 ± 206.3*	2446.9 ± 319.5*/†

* – the differences were statistically significant compared to the control group ($p < 0.05$)

† – the differences were statistically significant compared to the group II ($p < 0.05$)

Table 2. Maternal HRV parameters in the study population

Index	Group I	Group II	Group III
SDNN, ms	119. 8 ± 14.1	118.5 ± 28.2*	112.6 ± 24.3*/†
RMSSD, ms	46.6 ± 8.5	39.2 ± 11.6*	17.3 ± 6.1*/†
pNN5O, %	12.8 ± 3.2	12.3 ± 3.6*	2.1 ± 1.0*/†
AMo, %	34.6 ± 5.1	39.4 ± 10.8*	67.9 ± 18.1*/†
SI, c.u.	115.2 ± 16.8	243.7 ± 69.2*	1134.8 ± 285.4*/†
TP, ms^2	3084.6 ± 565.7	2351.2 ± 437.8*	905.2 ± 193.1*/†
VLF, ms^2	2361.2 ± 485.3	551.0 ± 192.6*	219.6 ± 67.8*/†
LF, ms^2	349.5 ± 42.6	1504.2 ± 563.9*	624.5 ± 124.6*/†
HF, ms^2	375.4 ± 56.1	296.2 ± 68.9*	62.1 ± 18.6*/†
LF/HF	0.9 ± 0.3	5.1 ± 1.6*	10.1 ± 3.0*/†

Notes: * – the differences were statistically significant compared to Group I ($p < 0.05$)

† – the differences were statistically significant compared to Group II ($p < 0.05$)

The maternal HRV in PE demonstrated an augmented activity of the central sympathetic circuit. This peculiarity was associated with the relative increase of AMo, SI and LF. It was indicated an abnormal pattern of gestational autonomic resetting. The mean sympatho-vagal balance (LF-to-HF ratio) values were 0.9 ± 0.3, 5.1 ± 6.6 and 10.1 ± 3.0 respectively in Group I, Group II and Group III. This gradual growth of sympatho-vagal balance was associated with the progredient severity of PE. The mean values of short-term parameters: the RMSSD, the pNN5O and the HF were lower in Group II and Group III. The lack of parasympathetic regulation and the dramatic decline of autonomic tone activity were explored in PE.

The relationship between RMSSD and sympatho-vagal balance was determined ($R = -0.56$; $p < 0.05$), RMSSD and TPVR ($R = -0.42$; $p < 0.05$), RMSSD and CI $R = 0.48$; $p < 0.05$) in pre-eclamptic patients.

Discussion

The obtained data supported the speculation that the decreased RMSSD was the main issue in pathogenetic pathway of cardiovascular maladaptation in PE [4, 10]. The growth of sympathetic domain region power was much more higher in PE than in healthy pregnancy in maternal horizontal position on her right side. The hypothesis that elevated intraabdominal pressure increases sympatho-vagal balance and decreases RMSSD could be done. Therefore, the additional pressure could contribute to strengthening of aortocaval compression and decreases the return of venous blood to maternal heart in PE. The emphasis on the preload requires sympathetic overactivity [5, 7, 10]. The above-mentioned autonomic modulations shift could suppress RSA. The explored negative correlation supported this speculation. The abnormally risen value of sympatho-vagal balance was associated with abdominal compartmentalization in severe PE [6].

The hyperdynamic circulation in mild-moderate PE was confirmed by augmented periferal vascular tone and increased cardiac output. Further transition to hypovolemia and low cardiac output manifested hypodynamic circulation in severe PE [9]. The increased sympathetic activity in the mild-moderate PE could contribute to better perfusion of end organ. The explored autonomic modulations were associated with gradual decrease of RSA. Severe PE was featured by dramatic sympathetic overactivity. High peripheral vascular resistance and hypovolemia caused hypoperfusion of end organ in severe pre-eclamptic patients. Therefore, the decreased RSA was a sign of cardiac failure.

The explored gradual decrease of RSA could help to determine the stages of hemodynamic disorders in women with PE. Therefore, the obtained data confirmed that RSA was related to pre- and afterload [1, 7, 9]. The normal or slightly reduced RMSSD value (35-45 ms), elevated CI and low TPVR were marked in patients with stage I. The application of β-blockers in order to modulate CI in combination with infusion of hydroxyethyl starch solutions could achieve hypervolemic hemodilution [8]. The support of the microcirculation in end organs was very relevant. The significant increase of TPVR was associated with low RMSSD value (25-34 ms) in women with stage II of hemodynamic disorders. The usage of nifedipine to reestablish vascular tone was rather evident. The infusion should be done very carefully with a small volume. The III stage was featured by very low RMSSD (15-24 ms), decreased SI and elevated TPVR. The hypervolemic hemodilution could not be achieved because of fluid redistribution, increased vascular permeability and crisis of microcirculation. The transition to final stage IV started with the onset of pulmonary oedema. Therefore, the ability to support maternal hemodynamics exists in pre-eclamptic patients with stage I or stage II within limited temporal period. The goal of the treatment is to prevent cerebral hemorrhage, stimulate fetal lungs maturation and in case of PE severity progression to prepare patient for immediate pregnancy termination. Possibly, the decrease of the intra-abdominal pressure could restore the autonomic balance and the level of RSA in puerperium.

Conclusion

Maternal RSA is an evident biophysical marker of PE and could be used as an additional criterion of its severity.

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