



## ANTIHYPERTENSIVE DRUGS IMPACT ON THE REGULATION OF MATERNAL AND FETAL CARDIAC ACTIVITY IN PREGNANT WOMEN WITH PREECLAMPSIA

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### ABSTRACT

*Preeclampsia is a serious complication of pregnancy that leads to maternal multiple organ failure and fetal growth retardation. The objective of the study was to investigate the parameters of cardiac activity of mother and fetus affected by antihypertensive therapy for pregnant women with preeclampsia. Types of central maternal hemodynamics based on bioimpedance cardiography, parameters of maternal heart rate variability and fetal electrocardiogram in 72 preeclampsia patients with 32-38 weeks of gestation were examined. The control group was comprised of 30 women with factors associated with physiological pregnancy. In the presence of mild preeclampsia, an increased capacity of the central and peripheral sympathetic regulation of the hemodynamics and almost constant power of the vagal tone were observed. These changes were essential for the hyperkinetic type of central maternal hemodynamics. In the presence of moderate and severe PE, relative hypersympathicotonia associated with reduced heart rate variability was observed. It was accompanied by generalized vascular spasm and decreased cardiac index.*

*The use of carvedilol has contributed to the correction of hypersympathicotonia with decreased autonomic balance in pregnant women with mild preeclampsia. The use of methyldopa and nifedipine has not had any normalizing effect on total spectrum and separate branches of maternal heart rate variability in pregnant women with moderate and severe preeclampsia. The effect of antihypertensive drugs on the fetal cardiac activity was also not determined.*

**KEYWORDS:** preeclampsia, maternal and fetal hemodynamics, antihypertensive therapy.

### INTRODUCTION

Preeclampsia (PE) is a disease associated with pregnancy and found only in humans. The cause of the disease is a complex systemic changes of maternal hemodynamics due to the damage of utero-placental circulation [Sibai BM, 2003; Hladunewich M et al., 2007; Lakhno IV, 2014]. An increased production of vasoconstrictor substances, pro-inflammatory cytokines and thrombophilia are likely to disrupt the natural gestational process of hypervolemic condition because of the reduced influence of the vagal-insular mechanisms of regulation [Voss A et al., 2006; Andrietti S et al., 2008; Maeda K, 2014]. It is believed that the activation of sympathetic-adrenal branch of the maternal autonomic nervous system plays a significant role in the

development of PE. Fetal sympathetic hyperactivity in PE was also observed [Swansburg ML et al., 2005; David M et al., 2007].

The study of maternal and fetal heart rate variability (HRV) allows estimating the level of regulation depending on the current requirements in providing trophic processes of the fetoplacental system [Brown CA et al., 2008]. The application of antihypertensive drugs contributes to the modifications in autonomic nervous regulation in its projections on hemodynamics. The usage of bioimpedance cardiography allows for a varied selection of antihypertensive agent in accordance with the type of the central maternal hemodynamics (CMH) [Sibai BM, 2003]. The antihypertensive drugs currently used in obstetrics have different mechanisms of action. They could penetrate into the fetus and change the regulatory state of the circulatory system [Swansburg ML, 2005].

One of the main antihypertensive drugs' modes of

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actions is the elimination of the central and peripheral mechanisms of vasoconstriction. The cause of practical interest is the possibility of pharmacological correction of hypersympatheticotonia and probable normalization of sympathetic-vagal balance.

The objective of this study was to investigate the parameters of maternal and fetal cardiac activity affected by antihypertensive therapy for pregnant women with PE.

#### MATERIALS AND METHODS

The study protocol was approved by the bioethics committee of the Kharkiv medical academy of postgraduate education. The subjects were informed about the methods of the study, its objective, indications and possible complications before inclusion in the study. All patients gave written informed consent to participate in the study.

The study involved a total of 102 pregnant women at 32-38 weeks of gestation, and 30 of them had had physiological gestation and comprised the Group I (control). Group II was comprised of 40 pregnant women with mild PE. Thirty two patients with moderate and severe PE formed Group III. In all the patients CMH types were investigated by bioimpedance cardiography on rheographic complex "Reocom" ("KhAI Medica" R&D center, Ukraine), maternal HRV and morphological parameters of fetal ECG were obtained from maternal abdominal 10-minute recordings using computer electrocardiographic system Cardiolab Baby Card" ("KhAI-Medica", Ukraine). The CMH investigation included determination of cardiac index (CI) and total peripheral vascular resistance (TPVR). The value of total power of the HRV spectrum (TP) and the power of the three spectral components were estimated: very low frequency (VLF), low frequency (LF) and high frequency (HF). The following temporal characteristics of the fetal HRV were investigated: SDNN (standard

deviation of normal to normal intervals), RMSSD (root mean square of successive differences), pNN50 (the proportion of the number of pairs of successive NNs that differ by more than 50 ms divided by total number of NNs), AMo (the amplitude of mode) (the number of cardiointervals, corresponding to the value of mode (or within modal interval) in % of the volume of the sample) and stress index, which was determined by the ratio of the height of the histogram to its width and characterizes the degree of tension of regulatory systems. The ECG recordings were obtained from maternal abdominal wall. The morphological parameters of fetal ECG were investigated: duration of intervals (ms) pQ, QT and QRS, amplitude (mV) of the T wave and the ratio of T/QRS. These instrumental studies were performed on the day of admission and 2-3 days after the beginning of therapy.

All examined patients with PE received antihypertensive drugs according to the type of CMH. The pregnant women with hyperkinetic type of CMH were administered carvedilol at 6.25-12.5 mg 2 times daily, in the eukinetic type – methyldopa 250-500 mg 4 times a day, and in hypokinetic type – methyldopa 500 mg 4 times daily combined with nifedipine 20 mg 2 times day.

The results were processed by parametric statistical methods (mean - M, error - m) using statistics software package Excel adapted for biomedical research.

#### RESULTS

The study of CMH types in healthy pregnant women revealed that the eukinetic type was observed in 93.3% of cases and the hyperkinetic in 6.7% of cases in Group I. The values of SI and TPVR were significantly different in pregnant women of main clinical groups demonstrating an increase in pre- and afterload on maternal heart in moderate and severe PE (Table 1). The predominant type of CMH was hyperkinetic in Group II, which accounted for 85.0% of

TABLE 1

The parameters of bioimpedance cardiography

Index, measurement units	Group I	Group II	Group III
Cardiac index, $l/min/m^2$	3.7±0.8	3.9±1.2*	2.1±1.1**
Total peripheral vascular resistance, $dyn.s/cm^5$	1218.5±146.4	1368.2±225.4*	2471.2±396.5**

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

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

cases. The eukinetic type of CMH was found in the remaining 15.0% of women with mild PE. The eukinetic type of CMH was observed in 78.1% of patients in Group III and 21.9% of patients had hypokinetic type. The obtained data indicate the presence of generalized vasoconstriction and the formation of heart failure in pregnant women with PE in Group III.

The study of maternal HRV has made it possible to determine some stability of its parameters in Group I and Group II (Table 2). Increased capacity of the central and peripheral sympathetic regulation of hemodynamics and almost constant power of vagal tone were observed in mild PE. These features were typical for hyperkinetic type of CMH. At the same time, patients with moderate and severe PE

exhibited reduction in total level of autonomic regulation and its separate parameters in the presence of a relative increase of the central sympathetic tone. It was noteworthy that the metabolic-humoral influences in the branch of VLF had decreased significantly. The most significant reduction in the capacity of HRV was determined in HF region. Therefore it may be assumed that vagal regulation participated in the pathogenesis of PE. An increase of maternal blood pressure and heart rate reduction in Group III was accompanied by a decrease in cardiorespiratory synchronization. In general, PE had a cardiodepressive impact on pregnant women.

The assessment of fetal ECG parameters in observed pregnant women allowed suggesting that in

TABLE 2.

Index, measurement units	Maternal HRV parameters		
	I	II	III
SDNN, ms	119.8±14.1	102.5±9.0*	82.6±10.4**/**
RMSSD, ms	41.0±8.5	40.8±10.2	16.3±4.8**/**
pNN50 %	12.8±3.2	6.5±1.9*	1.8 ±0.6**/**
AMo, %	34.6±5.1	40.6±9.2*	65.4±12.1**/**
Stress Index, c.u.	115.2±16.8	326.4±20.5*	1263.2 ± 202.5**/**
Total power, ms <sup>2</sup>	2524.6±565.7	2268.2±347.2*	840.3±86.9**/**
Very low frequency, ms <sup>2</sup>	1760.2±182.6	1761.8±181.4	542.1±65.2**/**
Low frequency, ms <sup>2</sup>	389.5±42.6	317.3±51.6*	243.2±48.5**/**
High frequency ms <sup>2</sup>	375.4±56.1	178.3±22.4*	55.4±16.1**/**

NOTES: \* – 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 3.

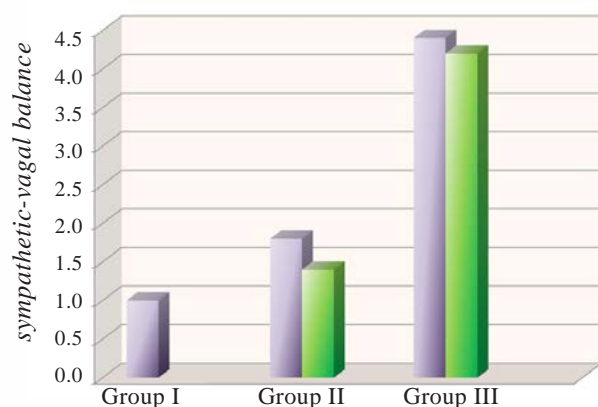
Values, measurement units	Fetal ECG parameters in observed patients		
	I	II	III
pQ, ms	101.9±16.3	108.5±17.6*	86.1±10.4**/**
QT, ms	202.4±28.6	190.6±31.4*	176.2±18.1**/**
QRS, ms	64.1±9.2	64.9±11.8*	65.4 ±12.3**/**
T, mcV	2.6±0.4	4.6±0.8*	7.8 ± 1.0**/**
T/QRS	0.04±0.01	0.07±0.02*	0.12±0.04**/**

NOTES: \* – the differences were statistically significant compared to the control group ( $p < 0.05$ );  
\*\* – the differences were statistically significant compared to the group II ( $p < 0.05$ ).

preeclamptic patients there were multiple-stage changes in the regulatory influences on fetal myocardium (Table 3). The possible increased catecholamine level was manifested in tachycardia and prolonged pQ in Group II. Further baroreflex activation has decreased fetal heart rate that was associated with the appearance of decelerations and has led to a relative shortening of the duration of pQ in Group III.

The reduction determined in the duration of the QT interval in Groups II and III was a reflection of the anaerobic metabolism appearance in the fetal myocardium caused by the activation of  $\beta$ -adrenergic receptors. The growth in the amplitude of the T wave and the increase in the T/QRS ratio were also due to the damaging effect of catecholamines on the fetal heart. The changes described were essential for the fetal distress in progress. Any significant differences from baseline in fetal ECG were not determined in the process of treatment.

The following changes were observed in the sympathetic-vagal balance during therapy (Fig). The values of this index were quite different and demonstrated the patterns of PE pathogenesis. In pregnant women with mild PE the increased sympathetic-vagal balance was due to the growth of sympathetic influences, but in Group III it was also associated with decreased activity of the vagal-insular regulation. The more significant changes affected by antihypertensive therapy occurred in Group II. At the same time, in this group in 42.5% of the women the type of CMH changed to eukinetic. Significant changes of the MCH type were not found in Group III.



**FIGURE** The value of the sympathetic-vagal balance in the examined patients prior to therapy (violet columns) and during therapy (green columns).

## Discussion

An increase in the activity of the sympathetic-adrenal regulation mechanisms was found in PE patients. So it was possible to speculate that absolute hypersympatheticotonia played the essential role in the mild PE pathogenesis, and relative hypersympatheticotonia – in moderate and severe PE. Multiple-stage hypersympatheticotonia connected with increased severity of PE was a consequence not only of the power absolute values growth in the region of LF, but, on the contrary, a moderate decline in the presence of significant reduction in TP, HF and VLF. The reduction in vasoactive-metabolic regulation was most expressed. This region of the HRV spectrum is traditionally associated with thermal regulation, the function of the hypothalamic-pituitary-adrenal axis and renin-angiotensin system activity [Voss A *et al.*, 2006; Tejera E *et al.*, 2012]. The reduced impact of sinus respiratory arrhythmia on maternal HRV in pregnant women with PE was a reflection of a tendency to loss of non-linearity in the cardiac activity and rigid rhythm formation. From this point, PE could be considered as a disease that has developed on the background of failure of adaptational hemodynamic mechanisms to the physiological gestational transformation.

The growth of sympathovagal balance in pregnant women with mild PE was accompanied predominantly with hyperkinetic hemodynamics. It is logical and explains the pathogenetic validity of the use of carvedilol. The subsequent decrease in autonomic balance has confirmed this thesis. In moderate and severe PE, the presence of relative hypersympatheticotonia with reduced HRV accompanied by generalized vascular constriction and decreased SI has precluded the usage of  $\beta$ -blockers without internal sympathomimetic activity. Therefore the usage of antihypertensive agents with a central mechanism of action and calcium antagonists was preferable [Sibai BM, 2003]. Nevertheless, antihypertensive therapy in Group III did not provide pronounced change in the type of CMH. It can be assumed that the use of methyldopa did not only contribute to a leveling of hypersympatheticotonia but also reduced the capacity of other regions of the autonomic nervous regulation spectrum.

The patients of group III influenced by maternal vasoconstrictors developed the deteriorated fetal condition. The influence of antihypertensive therapy on fetal ECG parameters has not been ascertained. In general, the development of fetal distress in pregnant PE women occurred under a different scenario, but the role of hypersympatheticotonia was also key.

#### CONCLUSION

Thus, pregnant women with mild PE have exhibited absolute hypersympatheticotonia, and those with moderate and severe PE – relative hy-

persympatheticotonia with predominant reduction of the total power spectrum, the vagal-insular and metabolic-vasoactive HRV regions.

The use of carvedilol has contributed to correction of hypersympatheticotonia and decreased autonomic balance in pregnant women with mild PE. The use of methyldopa and nifedipine has not had any clinically important normalizing effect on total power and separate branches of maternal HRV in pregnant women with moderate and severe PE.

The effect of antihypertensive drugs on the fetal cardiac activity has also not been determined.

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