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Decreased heart rate recovery in women with a history of pre-eclampsia

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ABSTRACT

Background: A growing body of literature has reported that a history of pre-eclampsia (PE) increases a woman's long-term risk of cardiovascular diseases (CVD). Autonomic nervous system dysfunction was found to be significant in this specific population, but most studies observed the role of sympathetic over-activation. The aim of this study was to assess whether parasympathetic impairment was involved in women 1 year after PE, and heart rate recovery (HRR) was used to represent parasympathetic tone.

Study design: 47 women with previous PE (PE group) and 58 women with a healthy pregnancy (control group) were examined. Blood pressure levels, lipid profiles, homeostasis model assessment of insulin resistance (HOMA-IR), inflammatory biomarkers and HRR were compared between the two groups, and the association between the biochemical parameters and HRR in the PE group was evaluated.

Results: Compared with the Control group, body mass index, 24-h mean diastolic blood pressure, low-density lipoprotein cholesterol and Ln(HOMA-IR) were higher, and HRR was slower in the PE group. Furthermore, body mass index, total cholesterol, and Ln(HOMA-IR) were independent determinants of HRR in the PE group according to multiple regression analysis.

Conclusions: Our findings suggest that parasympathetic impairment is involved in this specific female population, and its close association with body mass index, total cholesterol and insulin resistance might contribute to an increased risk of CVD development in women with PE history.

1. Introduction

Large cohort studies have consistently demonstrated an increased risk of cardiovascular diseases (CVD) later in life in women with a history of pre-eclampsia (PE) compared with women with a normal pregnancy, which is an almost 3-fold increased risk of hypertension and an approximately 2-fold increased risk of ischemic heart disease, stroke and venous thromboembolism [1,2]. Although the underlying mechanisms are still not well defined, some common traits, including sympathetic over-activation, insulin resistance (IR) and endothelial dysfunction, are confirmed as contributors to this increased risk [3,4].

As we know, autonomic dysfunction is commonly associated with CVD and has also been reported in subjects with risk factors for developing CVD. Autonomic dysfunction in these populations is mainly characterized by increased sympathetic activity and decreased parasympathetic activity, which increases cardiac load and raises vascular instability [5]. A previous investigation showed that the resting plasma norepinephrine level, a typical index of sympathetic tone, was higher in women 5–6 years after PE history than in women with a healthy pregnancy [6]. Similarly, it was revealed that muscle sympathetic nerve activity was elevated in women with a history of hypertensive pregnancy relative to controls [7]. However, few data focused on whether parasympathetic impairment was also involved in this specific population. Heart rate recovery (HRR), the quantification of heart rate (HR) decrease after exercise, is a useful, straightforward method and a highly reproducible tool for assessing parasympathetic activity [5]. Slower HRR has been identified as a powerful prognostic parameter for mortality in CVD patients [8]. In this respect, the study was designed to assess if there was a significant difference in HRR between women with a PE history and women with a healthy pregnancy history, and the association of HRR with some CVD traditional risk factors, such as lipid profile, IR, and inflammatory biomarkers.

2. Methods

2.1. Subjects enrollment

This case-control study was approved by the Ethics Committee of

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Shanghai Tenth People's Hospital Affiliated to Tongji University, and all participants gave their informed consents prior to information collection. Participants consisted of two groups: women with a PE history (PE group) and women with a normal pregnancy history (Control group). All of them, Han residents of Shanghai, attended the Department of Gynecology and Obstetrics in Shanghai Tenth People's Hospital from January 2015 to October 2017. The PE group comprised 47 women, who came for 1-year follow-up after the index pregnancy. Pre-eclampsia was defined as pregnancy-induced hypertension in a patient with proteinuria > 300 mg in a 24-h period or qualitative proteinuria > 1+ after 20 weeks of gestation in accordance with the guidelines of the American College of Obstetricians and Gynecologists [9]. Hypertension was defined as maternal systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg measured on two occasions separated by at least 6 h, arising *de novo* after gestation in a previously normotensive woman [9]. The Control group comprised 58 age-matched women who were also 1 year after delivery of a healthy pregnancy. None of the subjects had diabetes mellitus (including the development of gestational diabetes), impaired glucose tolerance or impaired fasting glucose, autoimmune diseases, thyroid dysfunction or any other endocrine disorder, secondary hypertension, severe hypertension (supine SBP > 180 mmHg or DBP > 110 mmHg), severe ventricular arrhythmia, severe atrioventricular block, severe reduction in left ventricular ejection fraction (LVEF ≤45%), valvular disease requiring surgery, severe renal dysfunction (i.e., creatinine > 2.5 mg/dl), severe orthopedic problems that would prohibit exercise, acute systemic illness such as fever, or the habit of smoking. Patients who were taking anti-hypertensive drugs or anti-dysrhythmic drugs such as β-blockers were excluded.

2.2. Ambulatory BP recordings

Ambulatory 24-h BP monitoring was performed using a SunTech Oscar2 ABPM recorder (Suntech Medical Inc., Morrisville, NC, USA). Automatic BP recordings were obtained every 30 min during the 24-h period. The cuff was placed around the non-dominant arm of the subjects. 24-h mean SBP and 24-h mean DBP were analyzed by a technician who was not aware of the subject's clinical history.

2.3. Laboratory tests

A venous blood sample was collected from each participant under fasting condition. Fasting blood glucose (FBG), insulin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), uric acid (UA), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor alpha (TNF-α) were measured using standard laboratory methods. The homeostasis model assessment of IR(HOMA-IR) was determined using the formula: HOMA-IR = [fasting glucose (mmol/l) × fasting insulin (uU/ml)]/22.5 [10].

2.4. HRR measurements

All subjects underwent an incremental cardiopulmonary exercise test (CPET) on a bicycle ergometer. To stabilize respiratory exchange, subjects were asked to remain still on the ergometer for at least 3 min before starting exercise. The CPET was performed according to a symptom-limited Bruce's protocol, with continuous electrocardiographic monitoring. Blood pressure (BP) was measured and recorded at rest, at the end of each stress stage, at peak stress and at recovery. The test was stopped for any of the following reasons: a rating of perceived exertion > 17 (Borg scale); achievement of > 90% of age-predicted maximum heart rate (HR); if the subject was too fatigued to continue the test safely; SBP > 200 mmHg; typical chest discomfort; severe arrhythmias; and more than 1 mm of horizontal or downsloping ST segment depression. After achieving peak exercise, the test was almost immediately terminated while the subjects were in the sitting position. The HRR was obtained by subtracting HR at the first minute of recovery from peak HR obtained during exercise. Therefore, the subjects in our CPET did not go through a "cool-down" phase. It was reported that the value of HRR might be affected by the small workload during the "cool-down" phase, decreasing its diagnostic sensitivity [11,12]. The whole process was supervised by a cardiologist and a nurse, who were unaware of the subject's clinical history.

2.5. Statistical analysis

Data were expressed as mean ± SD for numeric variables. A Student's *t*-test was used to evaluate differences between the two study groups. Non-normal distributed data was normalized to its natural logarithm. Pearson correlation coefficients were calculated to evaluate the relationship between clinical parameters, biochemical biomarkers and HRR. Variables that were significantly associated with HRR in the PE Group women were tested for independence by multivariated logistic regression analysis. A P value of < 0.05 from a two-sided test was considered statistically significant. All statistical analyses were performed using the software package SPSS, version 17.0 (SPSS Inc., Chicago, USA).

3. Results

The characteristics of the 2 groups were shown in Table 1. Both groups in the study were similar with regard to age, 24 h-mean SBP, ALT, AST, Cr, UA, TC, TG, HDL-C, FBG, insulin, hs-CRP, TNF-α and HRrest levels. BMI, 24 h-mean DBP, LDL-C and Ln(HOMA-IR) were higher in the PE group than those of the Control group ($P < 0.05$), while delivery at gestational weeks and HRR were smaller in the PE group than the Control group ($P < 0.05$).

Significant correlations between HRR and clinical parameters in the

Table 1
Demographic characteristics, biochemical parameters and HRR of 2 groups.

	PE Group (n = 47)	Control Group (n = 58)	*P*-value
Age (years)	31.2 ± 3.6	30.7 ± 4.1	0.27
Delivery at gestational weeks	36.1 ± 2.2	38.4 ± 1.6	0.04
BMI (kg/m^2)	23.7 ± 3.1	20.8 ± 1.9	0.03
24-h mean SBP (mmHg)	126.8 ± 10.7	121.0 ± 11.5	0.09
24-h mean DBP (mmHg)	85.4 ± 10.5	71.3 ± 8.6	< 0.01
ALT (U/L)	30.1 ± 7.4	28.2 ± 8.7	0.35
AST (U/L)	25.9 ± 5.4	26.3 ± 6.8	0.42
Cr (umol/L)	63.2 ± 11.7	59.5 ± 12.6	0.56
UA (umol/L)	325.4 ± 30.3	337.6 ± 35.8	0.31
TC (mmol/L)	4.6 ± 0.9	4.4 ± 0.7	0.28
TG (mmol/L)	1.1 ± 0.4	1.3 ± 0.3	0.53
HDL-C (mmol/L)	1.7 ± 0.3	1.6 ± 0.5	0.31
LDL-C (mmol/L)	3.8 ± 0.5	3.0 ± 0.6	0.02
FBG (mmol/L)	4.3 ± 0.8	4.4 ± 0.7	0.64
Insulin (uU/ml)	20.1 ± 5.1	19.4 ± 4.2	0.25
Ln(HOMA-IR)	1.22 ± 0.41	0.96 ± 0.37	0.03
hs-CRP (mg/L)	1.5 ± 0.4	1.3 ± 0.6	0.59
TNF-α (g/L)	0.7 ± 0.2	0.8 ± 0.3	0.43
HRrest (b/min)	78.3 ± 10.6	74.5 ± 9.4	0.37
HRR (b/min)	19.1 ± 5.3	23.4 ± 5.1	< 0.01

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FBG, fasting blood glucose; Ln, the natural logarithm transform; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitive C-reactive protein; TNF, tumor necrosis factor; HRrest, heart rate at rest; HRR, heart rate recovery.