Contribution of Dysfunction of Maternal Hemodynamics to Renal Impairment in Preeclampsia

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Key Words

Hemodynamic monitoring · Preeclampsia · Renal function · Glomerular filtration rate

Abstract

Aims: To investigate the contribution of dysfunction of maternal hemodynamics to renal impairment in preeclampsia (PE). **Methods:** Urinary protein excretion, serum creatinine, blood urea nitrogen, uric acid, and glomerular filtration rate were assessed in 571 pregnant women with PE in addition to and noninvasive hemodynamic monitoring. Patients were classified into two groups: PE with renal impairment (glomerular filtration rate <90 ml/min/ 1.73 m², $n = 161$) and PE with normal renal function ($n = 410$). Cut-off values for hemodynamic parameters were calculated using receiver-operating characteristic curve analysis. **Results:** Maternal systolic function and cardiac output parameters were low and peripheral resistance was high in the PE renal impairment group. Cut-off values for the hemodynamic parameters, cardiac index, cardiac output, systemic vascular resistance index, and systemic vascular resistance were 2.85 l/min/m², 5.25 l/min, $3,014.5$ dyn s cm⁻⁵ m² and $1,636.0$ dyn s cm⁻⁵, respectively, according to receiver-operating characteristics curves. **Conclusion:** Renal impairment in PE is associated with reduced maternal cardiac output and increased peripheral resistance.

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Introduction

Preeclampsia (PE) is characterized by maternal hypertension and proteinuria. Hypertensive disorders during pregnancy cause significant maternal and perinatal mortality and morbidity. Hypertension in pregnancy plays a key role in the cardiovascular diseases that accompany disorders of maternal hemodynamics [1].

PE is the most common glomerular disease worldwide [2], and it can induce significant renal impairment, characterized by an elevation of 24 h urinary total protein excretion and a reduction in glomerular filtration rate (GFR) [3, 4]. However, correlations between dysfunctions of maternal hemodynamics and renal impairment in PE have not been established.

We use noninvasive hemodynamic monitoring to analyze cardiovascular function in PE. The monitor can analyze hemodynamic parameters and evaluate circulatory system function [1]. This approach involves the use of impedance cardiography (ICG), which can be used to quantitatively measure the mechanical activity of the heart (blood) relative to its electrical activity. The basic principle of ICG is the direct measurement of

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baseline resistance, velocity index (VI), acceleration index (ACI), pre-ejection interval, ventricular ejection time and HR, with subsequent calculations of other hemodynamic parameters based on these measurements [5]. This technique allows quick and easy monitoring of cardiac function and peripheral resistance for clinical purposes.

The aim of this study was to investigate the contribution of dysfunctions of maternal hemodynamics to renal impairment in PE. Renal function was assessed by monitoring serum creatinine (Scr), blood urea nitrogen (BUN), and GFR (ml/min/1.73 m²), as calculated by the Modified Diet in Renal Disease (MDRD) formula [6].

Materials and Methods

Patients and Laboratory Methods

The Nanjing Maternity and Child Health Hospital in Nanjing, China, is a large maternity unit and is the largest maternity hospital in Jiangsu Province. Our study population comprised 571 patients with PE and singleton pregnancies who had undergone obstetric investigations and treatment at the hospital between 2005 and 2011. PE was defined as an increase in blood pressure to $\geq 140/90$ mm Hg at 20 weeks' gestation accompanied by urinary protein excretion (300 mg protein in a 24 h urine specimen) [7, 8].

Written consent was obtained from all women and the study was approved by the Research Ethics Committee. Specific exclusion criteria included a history of cardiac disease, renal disease, suspected chronic hypertension, chronic illness, long-term use of medications, and multiple pregnancies. Fetuses with chromosomal abnormalities, genetic syndromes and infection were also excluded.

We assessed the 24 h urine total protein excretion (mg), Scr ($\mu\text{mol/l}$), BUN (mmol/l), and GFR (ml/min/1.73 m²) in all subjects. The GFR estimation, according to the MDRD formula, was calculated as follows [9]: $\text{GFR} = 186 \times (\text{Scr } (\mu\text{mol/l}) \times 0.0113)^{-1.154} \times \text{age (years)}^{-0.203} \times (0.742) \times (1.210 \text{ if African-American})$.

As the GFR is more sensitive and accurate than other indicators, and is generally accepted as the best overall indicator of renal function, we divided the patients into two groups according to the GFR: PE with renal impairment (GFR < 90 ml/min/1.73 m²) [10, 11] and PE without renal impairment (GFR ≥ 90 ml/min/1.73 m²).

Hemodynamic Monitoring

All women underwent noninvasive hemodynamic monitoring using a BioZ ICG monitor (CardioDynamics, San Diego Calif., USA). After a rest period of 15 min, the women were examined in the lateral decubitus position. All measurements were performed by a single examiner (Hai-Qing Wu), according to the manufacturer's guidelines. The following parameters were monitored: heart rate (HR), mean arterial pressure (MAP), cardiac index (CI), cardiac output (CO), stroke index (SI), stroke volume (SV), systemic vascular resistance index (SVRI), systemic vascular resistance (SVR), ACI and VI.

Table 1. Demographic characteristics^a

Parameter	PE with renal impairment (n = 161)	PE without renal impairment (n = 410)
Maternal age, years	29.68 $\pm$ 4.71	29.48 $\pm$ 4.74
Maternal height, cm	160.22 $\pm$ 5.06	160.60 $\pm$ 4.55
Maternal weight, kg	74.04 $\pm$ 11.21	77.23 $\pm$ 11.18
Body surface area (BSA) ^b , m ²	1.77 $\pm$ 0.13	1.81 $\pm$ 0.13
Gestation at delivery, weeks	36.60 $\pm$ 2.92	37.63 $\pm$ 2.48
Birthweight, g	2,590.93 $\pm$ 821.61	2,954.02 $\pm$ 786.12

^a Values are presented as mean $\pm$ SD.

^b BSA estimation according to the DuBois formula: $\text{BSA (m}^2\text{)} = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$.

Statistical Analysis

Values are expressed as mean $\pm$ SD. Differences between mean values of hemodynamic variables in the PE groups were analyzed using the two-sample t test. A receiver-operating characteristic (ROC) curve was drawn and the area under the curve (AUC) was calculated to evaluate whether changes in hemodynamic parameters were predictive of renal impairment. The sensitivity, specificity and predictive values for hemodynamic parameters cut-off points were calculated. All statistical analyses were performed using SPSS software, version 17.0 (SPSS, Inc., Chicago, Ill., USA), apart from the scatterplot with a linear regression line, which was drawn using Stata software, version 9.0. $p < 0.05$ was considered statistically significant.

Results

Data was collected for all 571 women. Only 6 women (1.05%) with PE had an abnormal Scr and 33 women (5.78%) with PE had an abnormal BUN. There were 19 patients (3.33%) with a moderate impairment of renal function (≥ 30 GFR < 60 ml/min/1.73 m²) [10, 11] and 142 patients (24.88%) with mild renal impairment (≥ 60 GFR < 90 ml/min/1.73 m²) [10, 11] in the PE patients. A significant number of patients with PE had a decreased GFR, despite having a normal Scr and BUN. The comparisons between demographic characteristics of the patients with PE with a degree of renal impairment (GFR < 90 ml/min/1.73 m²) and those with PE without renal impairment are shown in table 1.

The maternal hemodynamics of the two groups were analyzed and compared, and the results are presented in table 2. The MAP, SVRI, and SVR values in the PE with renal impairment group were significantly higher than

Table 2. Maternal hemodynamics in the groups of patients with PE with or without renal impairment^a

Parameter	PE with renal impairment (n = 161)	PE without renal impairment (n = 410)	p
HR, bpm	89.30±14.55	93.62±14.18	0.001
MAP, mm Hg	123.46±13.95	111.70±12.65	0.002
CI, l/min/m ²	2.79±0.56	3.08±0.47	<0.001
CO, l/min	4.97±1.14	5.56±1.04	<0.001
SI, ml/m ²	31.95±7.18	33.34±5.65	0.015
SV, ml	56.66±13.88	60.22±11.46	0.002
SVRI, dyn s cm ⁻⁵ m ²	3,216.47±1,104.50	2,754.96±614.65	<0.001
SVR, dyn s cm ⁻⁵	1,839.45±666.96	1,539.24±373.82	<0.001
ACI, /100/s ²	84.87±31.37	88.24±30.28	0.236
VI, /1,000/s	44.21±15.96	47.34±13.15	0.016

^a Values are presented as mean ± SD.

those observed in the group without renal impairment. CO and CI values were markedly lower in the PE with renal impairment group than in the group without impairment. Variations in systolic cardiac function (SI, SV, and VI) values showed similar trends to those observed with CI and CO, which were markedly decreased in the renal impairment group. The ACI in the renal impairment group was slightly lower than that observed in the normal renal function group. The HR was similar in both groups. The CI, CO, SVRI, and SVR all showed a greater difference between the two groups than other hemodynamic parameters ($p < 0.001$). Figure 1a–d reveals the results of the ROC curve analysis. The area under the ROC curve (AUC) between CI and impairment in renal function was 0.654, while that between CO and renal impairment was 0.653. When an optimal cut-off value of 2.85 (l/min/m²) for CI was applied, sensitivity and specificity for PE with renal impairment were 54.0 and 68.3%, respectively; when an optimal cut-off value of 5.25 (l/min) for CO was applied, sensitivity and specificity for PE with renal impairment were 61.5 and 60.2%, respectively. In addition, the analysis indicated an AUC of 0.642 for SVRI and of 0.649 for SVR. A combination of maximum values of sensitivity and specificity was obtained with a SVRI of 3,014.5 (dyn s cm⁻⁵ m²). With this value, SVRI sensitivity was 53.4% and specificity was 71.0%. A combination of maximum values of sensitivity and specificity was obtained with a SVR of 1,636.0 (dyn s cm⁻⁵). With this value, SVR sensitivity was 58.4% and specificity was 66.3%.

Discussion

In this study of 571 women with PE, we found that 28.20% patients had a decreased GFR. This finding is consistent with other studies. Liu et al. [3] and Wang et al. [12] found that PE induced significant renal injury characterized by an elevation of 24 h urine total protein excretion and a reduction in GFR. Alsuwaida et al. [13] reported that an estimated GFR ranging between 60 and 89 ml/min/1.73 m² was associated with significant maternal and fetal complications.

Our results also revealed that a significant number of patients with PE had a decreased GFR, despite having a normal Scr and BUN. Although Scr may appear to be a simple tool for assessing renal function, it is influenced by age, gender, race, body size, diet, drugs, and laboratory methods. In addition, the normal range for Scr is lower in pregnancy and most laboratories report a normal range for the general population. The GFR is generally accepted as the best overall indicator of renal function and is therefore an important marker of renal disease. Both Scr and GFR are not linearly but hyperbolically related, and GFR can be impaired when Scr remains within normal limits.

Direct measurement of GFR involves exogenous substances such as inulin, nonradioactive contrast agents or radiolabelled compounds, and is not routinely performed in obstetrics. The majority of GFR estimates are based on creatinine values and the MDRD study equation for estimating GFR, which can be easily measured in obstetric patients. Many studies define moderate or mild renal impairment as ≥ 30 GFR < 60 ml/min/1.73 m² or ≥ 60 GFR < 90 ml/min/1.73 m² [10, 11, 14]. According to these criteria, we found that 28.20% of PE patients had moderate or mild renal impairment (GFR < 90 ml/min/1.73 m²).

Disturbances of maternal systemic hemodynamics in PE may contribute to renal impairment. Maternal cardiovascular parameters can be noninvasively measured using ICG. In a previous study, we found that peripheral resistance gradually increased and CO gradually decreased in the following order: normal pregnancy, pregnancy-induced hypertension and PE [1].

In this study, we explored the contribution of dysfunction of maternal hemodynamics to renal impairment in PE. The results revealed that maternal systolic function (SI, SV, and VI) and CI and CO parameters were low and peripheral resistance (SVRI and SVR) was high in the group of patients PE with renal impairment group compared to the normal renal function group. We also conducted a ROC analysis to identify hemodynamic parameters (CI, CO, SVRI, and SVR), which increased the risk of renal im-

Fig. 1. ROC curve analysis of CI, CO, SVRI, and SVR as hemodynamic parameters for PE with impairment of renal function. **a** CI: the corresponding AUC between CI and renal impairment was 0.654. With a specificity of 68.3%, sensitivity of CI for PE with renal impairment was 54.0%, at a cut-off value corresponding to 2.85 (l/min/m²). **b** CO: the corresponding AUC between CO and renal impairment was 0.653. With a specificity of 60.2%, sensitivity of CO for PE with renal impairment was 61.5%, at a cut-off value corresponding to 5.25 (l/min). **c** SVRI: the area under the ROC curve

between SVRI and renal impairment was 0.642. A combination of maximum values of sensitivity and specificity was obtained with a SVRI of 3,014.5 (dyn s cm⁻⁵ m²). With this value, SVRI sensitivity was 53.4% and specificity was 71.0%. **d** SVR: the area under the ROC curve between SVRI and renal impairment was 0.649. A combination of maximum values of sensitivity and specificity was obtained with a SVR of 1,636.0 (dyn s cm⁻⁵). With this value, SVR sensitivity was 58.4% and specificity was 66.3%.

pairment in PE (CI <2.85 l/min/m²; CO <5.25 l/min; SVRI >3,014.5 dyn s cm⁻⁵ m²; SVR >1,636.0 dyn s cm⁻⁵).

Maternal cardiovascular function changes markedly during pregnancy. In women with PE, the hemodynamic and vascular adaptations to pregnancy are disturbed. Preeclamptic women cross over from a high-output state to a high-resistance state and exhibit a marked decrease in CO and an increase in vascular resistance [15]. Rapid surges in blood pressure, which may overcome the kidney's capacity to prevent perturbations in renal hemodynamics, correlate closely with renal damage in hypertension [16]. Jeyabalan and Conrad [17], using a gravid rat as a model, found that in most women with PE, renal plasma flow (RPF) and GFR are decreased as a result of increased afferent arteriolar resistance and/or a reduced ultrafiltration coefficient. Therefore, disorders of maternal cardiovascular and systemic hemodynamics, particularly an inadequate maternal CO and a high peripheral resistance, may decrease RPF and GFR, with consequent renal impairment in women with PE.

It follows that, when treating patients with PE patients, we should pay attention to changes in cardiovascular and systemic hemodynamics. Once the hemodynamic parameters (CI, CO, SVRI, and SVR) exceed the cut-off values, we should be alert to renal impairment and address measures to increase CO and reduce peripheral vascular resistance in order to improve RPF and GFR.

Acknowledgments

This study was supported by grants from the National Natural Science Foundation of China (No. 81200442), the Natural Science Foundation of Jiangsu Province, China (No. BK2011106) and the Scientific and Technological Personnel Start Projects Foundation of Nanjing Health Bureau, Jiangsu Province, China (No. QYK11141).

Disclosure Statement

The authors have no conflicts of interest to disclose.

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