Effects of Shear Stress and Estradiol on Hypertension: Postprint

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Abstract

Background Low shear stress can induce vascular inflammatory responses, thereby contributing to the development and progression of hypertension. Estrogen can modulate the immune system and inflammatory responses through estrogen receptor-mediated pathways, exerting a protective effect against hypertension. Currently, deaths caused by cardiovascular diseases have become the leading cause of mortality among Chinese residents. This study aims to further understand the influencing factors of hypertension, thereby providing valuable guidance for the prevention of cardiovascular disease development.

Objective To understand the prevalence and influencing factors of hypertension in women, investigate the correlations between shear stress, estradiol, and hypertension in women as well as the effect of estradiol on hypertension under different shear stress conditions, and further explore the interaction effect between estradiol and shear stress on hypertension.

Methods A case-control study design was adopted. Patients diagnosed with essential hypertension were randomly selected from those attending Hunan Provincial People' s Hospital as the case group, and a subset of individuals from the non-hypertensive population was randomly selected as the control group. Data including demographic information, physical measurement indicators, and plasma biochemical test results were collected from all participants.

Results The study included a total of 584 participants, all female patients, comprising 288 individuals in the case group and 296 in the control group. Statistical analysis revealed that age, education level, BMI, menopause status, family history of hypertension, triglycerides, cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum uric acid, serum creatinine, blood urea nitrogen, cystatin-C, high-sensitivity C-reactive protein, estradiol, whole blood viscosity, and shear stress were influencing factors for hypertension occurrence; among these, estradiol was identified as a protective factor against

hypertension, with its protective effect being more pronounced under low shear stress conditions. The hypertension clinical prediction model constructed using population data demonstrated good fit, with high concordance between training and validation sets. Correlation analysis between estradiol and hypertension under shear stress stratification showed that in the low shear stress group, each unit increase in estradiol was associated with a 14% reduction in hypertension risk ($P<0.05$); however, in the high shear stress group, the protective effect of estradiol against hypertension was not significant. We found that shear stress and estradiol had an interactive effect on hypertension.

Conclusion Estradiol is a protective factor against hypertension; its protective effect is more pronounced under low shear stress conditions; shear stress and estradiol exhibit a multiplicative interaction effect on hypertension.

Full Text

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Abstract

Background: Low shear stress can induce vascular inflammatory responses, leading to the development and progression of hypertension. Estrogen can regulate the immune system and inflammatory response through estrogen receptor-mediated pathways, exerting a protective effect against hypertension. Cardiovascular disease has become the leading cause of death among Chinese residents. This study aims to further understand the influencing factors of hypertension to provide better guidance for preventing the occurrence and development of cardiovascular diseases.

Objective: To investigate the prevalence and influencing factors of hypertension in women, explore the correlation between shear stress, estradiol, and hypertension in women, examine the effect of estradiol on hypertension under different shear stress conditions, and investigate the interactive effect of estradiol and shear stress on hypertension.

Methods: A case-control study was conducted. Patients diagnosed with primary hypertension were randomly selected from Hunan Provincial People' s Hospital as the case group, and non-hypertensive individuals were randomly selected as the control group. Demographic data, physical measurement indicators, and plasma biochemical test results were collected for all participants.

Results: The study included 584 female participants, with 288 in the case group and 296 in the control group. Statistical analysis identified age, education level, BMI, menopause, family history of hypertension, triglycerides, cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, uric acid, serum creatinine, urea nitrogen, cystatin C, high-sensitivity C-reactive protein, estradiol, whole blood viscosity, and shear stress as influencing factors for hypertension. Estradiol was identified as a protective factor, with its protective effect being more pronounced under low shear stress conditions. The hypertension clinical prediction model developed from population data showed good fit, with high concordance between training and validation sets. Stratified analysis by shear stress revealed that in the low shear stress group, each unit increase in estradiol reduced the risk of hypertension by 14% ($P<0.05$), while in the high shear stress group, the protective effect of estradiol was not significant. An interactive effect between shear stress and estradiol on hypertension was observed.

Conclusion: Estradiol is a protective factor against hypertension, with greater protective effects under low shear stress conditions. There is a multiplicative interaction between shear stress and estradiol on hypertension.

Keywords: Estradiol; Shear stress; Hypertension; Interaction; Vascular inflammation

Introduction

Hypertension is a chronic disease characterized by arterial systolic pressure $ $140 mmHg and/or diastolic pressure $ $90 mmHg at rest, often accompanied by functional or organic changes in organs such as the heart, blood vessels, brain, and kidneys [1]. As a syndrome primarily manifested by elevated blood pressure, hypertension is commonly associated with structural and functional damage to the heart, brain, kidneys, blood vessels, and retina, and remains one of the leading causes of cardiovascular disease and death [2].

Vascular inflammation represents a crucial mechanism in hypertension pathogenesis. Research has demonstrated that genes can regulate the risk of hypertension by modulating vascular inflammation. Cross-sectional studies have also found that changes in inflammatory factors in the serum of prehypertensive individuals and patients with essential hypertension indicate that vascular endothelial inflammatory injury exists even in the prehypertensive stage, with inflammation progressively worsening as the disease advances [3]. Therefore, controlling

vascular inflammatory responses and reducing inflammation severity may help prevent hypertension.

Shear stress is the tangential force generated by the interaction between blood flow and vessel walls, primarily influenced by blood viscosity ( ), blood flow rate (Q), and vessel diameter (r) [4]. Shear stress plays a pivotal role in atherosclerosis development, with low shear stress facilitating atherosclerotic plaque formation or rupture, while high uniform fluid shear stress offers protective effects against atherosclerosis [5]. Shear stress can also induce inflammatory responses and is associated with various inflammatory diseases. Researchers have found that low shear stress significantly enhances CX3CR1 expression and monocyte adhesion, whereas physiological laminar shear stress suppresses CX3CR1 expression [6]. Furthermore, studies have shown that low shear stress and oxidative stress activate signaling pathways that stimulate CRP and MMP-9 expression, induce vascular inflammatory responses, cause endothelial injury, and ultimately promote hypertension development and progression [7].

Estrogen, one of several sex steroid hormones, regulates the body through estrogen receptors [8]. Compared with men, young women are protected by estrogen against hypertension development and adverse cardiovascular outcomes [9]. Estrogen exerts antihypertensive effects primarily through direct action, influence on vascular endothelial function, effects of estrogen metabolites, antagonism of oxidative stress, and inhibition of vascular remodeling [10]. Additionally, estrogen possesses anti-inflammatory properties and can regulate the immune system and inflammatory response through estrogen receptor-mediated pathways [11]. Studies have shown that physiological-dose estrogen therapy after cerebral ischemia significantly suppresses pro-inflammatory cytokine production and release, downregulates pro-inflammatory factor expression, and inhibits production of neutrophil chemokines CXCL1, CXCL2, and CXCL3 in ischemic regions, preventing excessive neutrophil infiltration in the brain [12]. These findings suggest that estrogen may protect against hypertension by suppressing cellular inflammatory responses.

Currently, research on estrogen' s role in low shear stress-induced hypertension remains limited. This study aims to investigate the correlation between shear stress, estradiol, and hypertension in women, examine the effect of estradiol on hypertension under different shear stress conditions, and explore the interactive effect of estradiol and shear stress on hypertension.

1.1 Subject Selection

The study population consisted of female patients from the cardiology inpatient department of Hunan Provincial People' s Hospital between January 2021 and August 2021. Exclusion criteria included: (1) severe hematological, cardiac, renal, or hepatic diseases, or malignant tumors; (2) infectious diseases such as hepatitis B or tuberculosis; (3) recent use of medications affecting hormone or

lipid levels, or use of sex hormones, fibrinolytic, or anticoagulant drugs; (4) lactating or pregnant women. From patients diagnosed with primary hypertension (according to the 2018 Hypertension Guidelines), 288 individuals were randomly selected as the case group, while 296 non-hypertensive individuals were randomly selected from the physical examination department as the control group.

1.2 Data Collection

A self-designed questionnaire was administered through one-on-one interviews. The questionnaire included demographic characteristics (age, education level, etc.), lifestyle and dietary habits (smoking history, alcohol consumption, exercise time, etc.), past medical history and family history, and female reproductive history (menopause status, childbirth history, age at childbirth, etc.). Physical measurements included height, weight, BMI, heart rate, and waist circumference.

Laboratory tests included hormone indicators (estradiol), lipid levels [triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total protein (TP)], blood urea nitrogen (BUN), serum creatinine (Ser), uric acid (UA), cystatin C (Cys C), maximum shear rate (SR-max = PSV $\times$ 2/vessel radius), and hematocrit (HCT). Vascular ultrasound was used to detect vascular shear rate. Blood viscosity was calculated using the low shear rate blood viscosity formula: WBV = (1.98 $\times$ HCT) + 3.76 $\times$ (TP - 78.42), and shear stress was then calculated as: shear stress = shear rate $\times$ blood viscosity [13, 14].

1.3 Statistical Analysis

Data analysis was performed using SPSS 20.0 statistical software. Categorical data were described using percentages and compared using chi-square tests. Continuous data were expressed as mean $\pm$ standard deviation and compared using independent samples t-tests. Univariate chi-square and t-tests were first conducted to identify hypertension risk factors, followed by binary logistic regression analysis for significant variables. The median shear stress value was calculated to divide participants into high and low shear stress groups. Binary logistic regression and trend tests were used to analyze the relationship between plasma estradiol, shear stress, and blood pressure. R software was used to establish a clinical prediction model, with the ROCK package used to plot ROC curves and analyze the interaction between estradiol and shear stress. $P < 0.05$ was considered statistically significant.

1.4 Ethics Statement

This study collected population data according to the research methods approved by the National Natural Science Foundation of China project (81773530)

and was reviewed and approved by the Medical Ethics Committee of Hunan Normal University (2017034). Informed consent was obtained from all participants before questionnaire administration.

2.1 Univariate Analysis of Hypertension Risk Factors

The study included 584 female participants with a mean age of 67.68 ± 10.33 years. Univariate analysis of hypertension risk factors revealed statistically significant differences in age, education level, BMI, menopause status, and family history of hypertension ($P < 0.05$) . Among plasma biochemical indicators, significant differences were observed in triglycerides, cholesterol, LDL-C, HDL-C, uric acid, serum creatinine, urea nitrogen, cystatin C, estradiol, whole blood viscosity, and shear stress ($P < 0.05$), while hematocrit and total protein showed no significant differences. The hypertension group had higher mean age, lower education level, higher proportion of overweight and obese individuals, higher proportion of postmenopausal women, and higher proportion of individuals with family history of hypertension compared to the non-hypertensive group. No statistically significant differences were found for smoking or alcohol consumption ($P > 0.05$). Plasma biochemical tests showed that the mean estradiol level in the hypertension group was 12.95 ± 7.82, significantly lower than the 32.19 ± 31.87 in the non-hypertensive group ($P < 0.05$). Similarly, mean shear stress in the hypertension group was 5.37 ± 2.43, significantly lower than the 9.10 ± 1.31 in the non-hypertensive group ($P < 0.05$). These findings indicate that hypertensive individuals have lower estradiol and shear stress levels compared to normotensive individuals.

2.2 Binary Logistic Regression Analysis of Hypertension Risk Factors

Using hypertension status (yes = 1, no = 0) as the dependent variable and age, education level, BMI, alcohol consumption, menopause, smoking, triglycerides, cholesterol, LDL-C, HDL-C, urea nitrogen, serum creatinine, uric acid, cystatin C, estradiol, shear stress, and whole blood viscosity as independent variables, binary logistic regression analysis was performed. The results showed that age, education level, menopause, family history of hypertension, BMI, triglycerides, cholesterol, LDL-C, uric acid, serum creatinine, urea nitrogen, cystatin C, and whole blood viscosity were risk factors for hypertension. Each unit increase in estradiol reduced hypertension risk by 14% (OR = 0.861, 95% CI [0.826, 0.899], $P < 0.001$), with a statistically significant trend of decreasing hypertension risk as estradiol levels increased. Each unit increase in shear stress reduced hypertension risk by 72% (OR = 0.283, 95% CI [0.208, 0.385], $P < 0.001$), also showing a statistically significant trend of decreasing hypertension risk with increasing shear stress levels.

2.3 Clinical Prediction Model for Hypertension

Data with statistical significance from the binary logistic regression analysis were used to develop a nomogram for hypertension [Figure 1: see original paper]. Model validation [Figure 2: see original paper] showed high concordance between training and validation sets in the calibration curve, indicating good fit. The ROC curve for the clinical prediction model [Figure 3: see original paper] showed an area under the curve of 0.907 ($P < 0.001$), with sensitivity of 79.60% and specificity of 87.90%.

2.4 Correlation Analysis Between Estradiol and Hypertension Under Shear Stress Stratification

Based on shear stress values from 584 patients, the median shear stress of 8.21 dyne/cm^2 was used to divide participants into low shear stress ($ 8.21dyne/cm^{2})andhighshearstress(> 8.21dyne/cm{2}$) groups. In the low shear stress group, each unit increase in estradiol reduced hypertension risk by 14% in Model 1 (OR = 0.865, 95% CI [0.791, 0.946], P = 0.001) and by 19% in Model 2 (OR = 0.810, 95% CI [0.719, 0.914], P = 0.001), with both models showing statistically significant trends (P = 0.001). In Model 3, each unit increase in estradiol reduced hypertension risk by 16% (OR = 0.840, 95% CI [0.704, 1.002], P = 0.053), showing a trend of decreasing hypertension risk with increasing estradiol, though this trend was not statistically significant. In the high shear stress group, only Model 1 showed a statistically significant trend test (P = 0.041), but the reduction in hypertension risk with increasing estradiol was not significant .

2.5 Interaction Analysis Between Shear Stress and Estradiol

Analysis of the interaction between shear stress and estradiol revealed a multiplicative interaction with ORmultiplicative = 7.253 (95% CI [1.012, 13.494]). The OR value greater than 1 indicates a statistically significant multiplicative interaction, as illustrated in [Figure 4: see original paper].

3.1 Protective Effect of Estradiol on Hypertension

Recent research has identified estrogen as an important protective factor in blood pressure regulation. In the vascular system, estrogen regulates vascular

function and endothelial growth and apoptosis [15-17]. The rapid regulatory effects of estrogen on vascular function are typically manifested as endothelium-dependent vasoconstriction or vasodilation [18,19]. Studies have shown that long-term estrogen replacement therapy in ovariectomized rat models can prevent estrogen deficiency-induced cardiomyocyte apoptosis through death receptor and mitochondrial pathways, suggesting a protective role of estrogen against cardiovascular injury. Angiotensin II (Ang II) is a potent vasoconstrictor that promotes blood pressure elevation. Research indicates that estrogen can reduce Ang II production and decrease angiotensin II type 1 receptor levels, thereby altering renin-angiotensin-aldosterone system activity and mitigating blood pressure increases [20]. Epidemiological studies demonstrate gender differences in hypertension prevalence, with premenopausal women having lower hypertension rates than age-matched men, while postmenopausal women show rapidly increasing rates that exceed those of men. In summary, estrogen plays a crucial role in hypertension risk.

In this study, we found that individuals with normal estradiol levels had a 20% lower risk of hypertension compared to those with estradiol deficiency ($P < 0.001$), confirming that estrogen is a protective factor against hypertension.

3.2 Relationship Between Shear Stress and Hypertension

Hypertension development is closely associated with vascular endothelial cell dysfunction. Endothelial stability depends on multiple factors including blood pressure, blood glucose, and electrolyte balance, with shear stress being a critical determinant. Studies have shown that shear stress regulates endothelial barrier function through morphological changes [21], induces vasoconstriction through endothelial bioactive substances (NO) [22], and affects vascular inflammatory responses through differential expression of inflammatory markers [23]. Research demonstrates altered carotid hemodynamic parameters in hypertensive patients, including increased carotid intima-media thickness, increased blood viscosity, and changes in vessel diameter and blood flow velocity, which consequently alter shear stress, indicating an inseparable relationship between hypertension and shear stress [24]. Moreover, numerous experiments have proven that low shear stress enhances pro-inflammatory gene and protein expression [25], promotes atherosclerotic plaque and thrombus formation [26-27], thereby inducing vascular inflammatory responses and accelerating hypertension progression.

In this study, multivariate logistic regression analysis comparing shear stress data between hypertensive and non-hypertensive groups revealed that each unit increase in shear stress reduced hypertension risk by 72% (OR = 0.283, 95% CI [0.208, 0.385], $P < 0.001$), with a statistically significant trend of decreasing hypertension risk as shear stress levels increased. These findings suggest that low shear stress is a risk factor for hypertension development and progression.

3.3 Combined Effects of Shear Stress and Estradiol on Hypertension

After stratifying by median shear stress, the protective effect of estradiol on hypertension differed between strata. In the low shear stress group, estradiol demonstrated a more pronounced protective effect against hypertension that exceeded its protective effect in the overall study population, whereas in the high shear stress group, this protective effect was not significant and the difference lacked statistical significance.

Experimental data have shown that low shear stress can induce inflammatory responses through NF- B pathway activation [28], which is closely related to atherosclerosis pathogenesis. Estrogen plays an important role in suppressing inflammatory factors, oxidative stress, and premature aging by binding to estrogen receptors (ER) in various diseases [29]. Studies have demonstrated that estrogen can inhibit I Bα protein phosphorylation through ERβ, thereby blocking NF- B nuclear translocation and subsequent inflammatory activation [30], achieving anti-inflammatory and endothelial protective effects. In this study, we found a statistically significant multiplicative model for the interaction between estradiol and shear stress, indicating that estradiol and shear stress interactively affect hypertension. This suggests that shear stress and estrogen may coordinately regulate vascular inflammatory responses through the NF- B pathway.

3.4 Limitations

This study has several limitations. The inclusion and exclusion criteria did not consider whether participants had recently taken medications affecting shear stress, such as beta-blockers. Additionally, cell or animal experiments could be conducted to validate the study findings and provide further completeness.

Through this study, we found that plasma estradiol and high shear stress can reduce hypertension risk. When shear stress is low, the effect of estradiol in suppressing hypertension is more pronounced. We conclude that shear stress and estradiol have an interactive effect on hypertension.

Data Availability Statement

As this study is funded by the National Natural Science Foundation of China and the project is ongoing, the analyzed dataset is not currently publicly available but can be provided by the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.