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Does mild preeclampsia cause arterial stiffness and ventricular remodeling through inflammation?

Czy łagodny stan przedrzucawkowy powoduje sztywność tętnic i przebudowę komory serca poprzez zapalenie?

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Abstract

Background: *A link between preeclampsia (PE) and excessive maternal morbidity and mortality is a commonly recognized fact. Moreover, it has been suggested that chronic inflammatory state connected with PE contributes to accelerated atherosclerosis. There is also an association between PE and maternal cardiac remodeling and biventricular diastolic dysfunction. The aim of the study was to investigate the presence of impaired myocardial performance and increased arterial stiffness in patients who experienced a mild case of PE five years previously.*

Methods: *The study included forty PE patients (40 women; mean age 33.75±7.95) and 27 healthy volunteers (27 women; mean age 36.44±10.45)Transthoracic echocardiography, including Doppler echocardiography combined with tissue Doppler imaging (TDI), and aortic stiffness index (AoSI), aortic distensibility (AoD), and aortic elastic modulus (AoEM) values were measured in each study participant.*

Results: *There was a statistically significant increase in hsCRP, aortic stiffness index, and aortic elastic modulus in PE patients as compared to controls (2.43±1.91 vs. 3.80±2.06, p=0.007; 3.09±2.41 vs. 7.32±6.89, p=0.001; 2.89±2.11 vs. 7.00± 6.83, p=0.001), while a significant decrease was observed in the aortic strain and distensibility (respectively, 22.35±15.99 vs. 12.24±9.22, p=0.005; 11.17±9.68 vs. 6.13±4.99, p=0.018). No differences between the two groups were observed with regard to the left ventricular myocardial performance index (MPI) (0.55± 0.16 vs. 0.53± 0.19, p= 0.630).*

Conclusions: *To the best of our knowledge, this has been the first study to demonstrate impaired aortic elasticity and unaffected myocardial performance index in patients with mild PE. Moreover, these effects turned out to be significantly correlated with inflammation.*

Key words: **preeclampsia** / **arterial stiffness** / **ventricular dysfunction** /

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Streszczenie

Wstęp: *Istnieje powiązanie pomiędzy stanem przedrzucawkowym (PE) a nadmierną zachorowalnością i śmiertelnością. Ponadto, sugeruje się, że przewlekły stan zapalny udzielający się w PE przyczynia się do przyspieszenia miażdżycy. Istnieje również związek między PE przebudowy mięśnia sercowego ze strony matki i dwukomorową dysfunkcją rozkurczową. Zaplanowaliśmy ocenić w tym badaniu, czy nie została osłabiona wydolność mięśnia sercowego oraz zwiększenie sztywności tętnic u pacjentek, które pięć lat wcześniej miały łagodny przypadek PE.*

Metody: *W badanie włączonych zostało czterdzieści pacjentek (40 kobiet; średnia wieku 33,75±7,95) oraz 27 zdrowych ochotniczek (27 kobiet: średnia wieku: 36,44±10,45). Każda*

z pacjentek została zbadana za pomocą echokardiografii przezklatkowej, w tym echokardiografii dopplerowskiej w połączeniu z tkankową echokardiografią dopplerowską (TDI). Zostały również zmierzone takie wartości, jak wskaźnik sztywności aorty (AoSI), rozciągliwość aorty, a także moduł sprężystości aorty (AoEM).

Wyniki: *Stwierdzono statystycznie istotny wzrost hsCRP, wskaźnika sztywności aorty i modułu sprężystości aorty u pacjentów z PE w porównaniu z grupą kontrolną (2,43±1,91vs. 3,80±2,06, p=0.007; 3,09±2,41 vs. 7,32±6,89, p=0,001; 2,89±2,11 vs. 7,00± 6,83, p=0,001), natomiast znaczne zmniejszenie zaobserwowano w odkształceniu aorty i jej rozciągliwości (odpowiednio 22,35±15,99 vs. 12,24±9,22, p= 0,005; 11,17±9,68 vs. 6,13±4,99, p=0.018). Nie wystąpiły różnice pomiędzy tymi dwoma grupami w odniesieniu do wskaźnika wydolności mięśnia sercowego lewej komory (0,55± 0,16 vs 0,53± 0,19, p=0,630).*

Wnioski: *Stwierdziliśmy po raz pierwszy w tym badaniu, że wystąpiły osłabiona elastyczność aorty i niezmieniony wskaźnik wydolność mięśnia sercowego (MPI) u pacjentek z łagodnym PE, ponadto, efekty te były znacząco skorelowane ze stanem zapalnym.*

Słowa kluczowe: **łagodny stan przedrzucawkowy** / **sztywność tętnic** / / **wskaźnik wydolność mięśnia sercowego (MPI)** /

Introduction

Preeclampsia (PE) constitutes one of the most significant causes of maternal morbidity and mortality, affecting between 3-5% of all pregnancies [1], and is characterized by abnormal general vascular dilatation [2]. Endothelial dysfunction is the primary cause of impaired circulatory homeostasis in PE [3].

Recent studies have demonstrated PE-affected patients to face a great risk of developing cardiovascular diseases in later years [4,5,6]. Increased aortic stiffness and/or decreased aortic distensibility might be reflecting a widespread atherosclerosis. With adjustment for aging and blood pressure, previous studies demonstrated coronary artery disease, cerebrovascular disease, and extra-coronary atherosclerosis to be associated with increased aortic stiffness [7].

AoD(aortic distensibility), AoSI(aortic stiffness index), AoEM(aortic elastic modulus), tissue Doppler echocardiography and myocardial performance index(MPI) are used to assess different aspects of heart diseases. Each of these tests is already considered to be predictive of cardiovascular events, but combining them may yield an even higher predictive value. In our study we intended to detect whether MPI and aortic stiffness were impaired in PE patients without cardiovascular risk factors. Long-term effects of mild PE (mild preeclampsia is classified as a blood pressure (BP) of 140/90 mm Hg or higher with proteinuria of 0.3-3g/day) on MPI and arterial stiffness, which constitute important predictors of cardiovascular diseases that may develop later, remain poorly investigated due to a lack of MPI and arterial stiffness measurements [8].

Our assumption was that PE, which is a cause of several cardiovascular complications, may lead to arterial stiffness, as well as to impaired myocardial systolic and diastolic functions.

Methods

Study population

The study group included 40 patients (aged 18-40) who had been afflicted with PE five years previously. The control group consisted of 27 healthy women, matched for age and with comparable BMI (Body Mass Index), with no history of pregnancy-associated hypertension. Renal or systemic diseases, hypertension and hyperlipidemia, smoking, diabetes, glucose intolerance, thyroid dysfunction, chronic alcohol use, coronary artery disease or congenital heart disease, valvular heart disease, non-sinusoidal rhythm in the electrocardiogram, BMI >35 kg/m2 or a left ventricular mass index (LVMI) >110 g/m2, family anamnesis of coronary artery disease, breastfeeding, and heavy cases of PE (including the HELLP syndrome) before 37 weeks of pregnancy, constituted exclusion criteria from the study.

The study was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all study participants and Local Ethics Committee approved of the study protocol (KA09/372).

Age, gender, BMI, levels of fasting blood glucose, serum transaminase enzyme, serum uric acid, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride of the subjects were recorded. Using original kits with Abbott-Aeroset auto-analyzer (Chicago, IL, USA), fasting blood glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride levels were measured. Using the Abbott-Aeroset auto-analyzer (Chicago, IL, USA) and a highly sensitive sandwich Elisa technique, the plasma levels of C-reactive protein were also determined.

Echocardiographic examination

Each case was assessed using an Acuson Sequoia C256® Echocardiography System, equipped with a 3V2c broadband

transducer with second harmonic capability (Acuson, Mountain View, CA, USA). In the lateral decubitus position, two-dimensional, M-mode standard and 'pulsed' tissue Doppler echocardiography was performed in each subject. The echocardiographic images were recorded on VHS videotapes.

The left ventricular mass index (LVMI) and left ventricular ejection fraction (EF) were calculated using conventional formulas. Using pulse Doppler, volume samples were taken from the mitral and tricuspid valve tips. Early diastolic peak flow velocity (E), late diastolic peak flow velocity, the E/A ratio and E wave deceleration time (DT) were measured in transmitral Doppler imaging. The Tissue Doppler Imaging (TDI) program was set to the pulse wave Doppler mode. Other measurements were performed to show the regional systolic function. The measured values included peak velocity (cm/s), time-velocity integral of the myocardial systolic wave (Sm), myocardial early (Em) and late (Am) peak velocities (cm/s), the Em/Am ratio, and the Sm-Em time (left ventricular isovolumic relaxation time; IVRT).

In the diastolic measurements, the time interval was defined from the end of Sm to the beginning of Em. The left-ventricular ejection time (ET) was measured from the beginning of the left ventricular outflow to its end. The left ventricular isovolumetric contraction time (IVCT) is the time between the end of the mitral inflow and the beginning of the left ventricular outflow. The myocardial performance index of the left ventricle (MPI) was calculated according to the formula:

(IVCT+IVRT)/ET [9].

All the conventional echocardiographic and TDI parameters were determined by calculating the average of measurements in three consecutive cardiac cycles. The echocardiographic examination was evaluated by the same researcher, blinded to the clinical findings. Two other cardiologists, blinded to the cases, evaluated the echocardiographic recordings.

Aortic Distensibility and Stiffness Calculations

Internal dimensions of the transverse aortic arch were measured by a single operator in at least three consecutive cardiac cycles. The measurements were performed in the proximal ascending aorta, 3 cm away from the origin of the aorta. The following formulas were used to calculate AoD, AoSI and AoEM: [10].

Aortic distensibility: $[(D_s-D_d)/D_d]/dP$.

Aortic stiffness index: $Ln(P_s-P_d)/[(D_s-D_d)/D_d]$.

Elastic modulus: $dP/[(D_s-D_d)/D_d]x100$.

Where D_s is aortic diameter at systole, D_d is aortic diameter at diastole, dP is systolic-diastolic pressure change, Ln is logarithm base n, P_s is systolic blood pressure, and P_d is diastolic blood pressure.

Statistical analysis

SPSS software (Statistical Package for Social Sciences, version 10.0) was used to carry out the statistical analyses. The continuous variables were expressed as mean ± standard deviation (SD), and the categorical variables were expressed in the form of percentages. To test the normality of the distribution, the Kolmogorov-Smirnov test was used. Comparing the groups, the Student t-test was used for continuous variables and the Chi-square test for categorical variables. Pearson's correlation test was used to seek correlations. Values of $p < 0.05$ were considered to be statistically significant.

Results

Clinical characteristics of the study population

Table 1 shows general characteristics and risk factors of the study population for coronary artery disease. The two groups were similar with regard to age, BMI, heart rate, systolic blood pressure, diastolic BP, and uric acid levels, lipid profiles, and fasting glucose levels. In the PE group, high-sensitivity C-reactive protein (hsCRP) levels were higher (3.80±2.06 vs. 2.43±1.91; p= 0.007) as compared to controls.

Analysis of the echocardiographic measurements

The PE group and the controls were similar with regard to the left ventricular ejection fraction (EF), the left atrial diameter (LAD), and LVMI (Table 2).

Standard and tissue Doppler echocardiographic analyses

The two groups were similar with regard to mitral E-wave, mitral A-wave, mitral E-wave DT, mitral IVRT and the E/A ratio (Table II). As for the tissue Doppler echocardiographic analyses, the two groups were similar as far as the standard Doppler parameters were concerned. Likewise, no difference was found between the groups in systolic (Sm), early (Am), and late (Em) diastolic waves in their ratio (Em/Am), in IVRT and IVCT, as well as in the myocardial performance index (MPI) and E/e' (Table II).

Analysis of the aortic parameters

The two groups were similar with regard to systolic and diastolic aortic diameters (2.79±0.42 vs. 2.80±0.32; 2.51±0.45 vs 2.32±0.42. p>0.05). PE patients were marked by lower aortic strain (12.24±9.22 vs. 22.35±15.99; p=0.005) and AoD (6.13±4.99 vs. 11.17±9.68; p=0.018). and higher AoSI (7.32±6.89 vs. 3.09±2.41. p=0.001) and AoEM (7.00±6.83 vs. 2.89±2.11. p=0.001) as compared to controls (Table 3).

The relationship between hsCRP and other study variables

There was a negative correlation between hsCRP on the one hand and the aortic strain (r=-0.418; p=0.007), aortic distensibility (r=-0.446; p=0.004), and Sm (r=-0.312; p=0.005) on the other, and a positive correlation between hsCRP on the one hand and aortic stiffness index (r=0.396; p=0.012), aortic elastic modulus (r=0.365; 0.021), and mitral maximum IVRT (r=0.340; p=0.032) on the other (Table 4).

Reproducibility of the echocardiographic measurements

For all measurements, the intraobserver and interobserver regression coefficients were found to be 0.891 ($p<0.001$) and >0.912 ($p<0.001$), respectively.

Discussion

To the best of our knowledge, our study has been the first attempt to investigate the presence of impaired aortic elasticity and unaffected myocardial performance index in patients with mild PE. Moreover, these effects turned out to be significantly correlated with inflammation.

Epidemiological studies have recently shown a link between preeclampsia and increased risk of cardiovascular diseases in later years [6, 1, 12]. Besides, the risk of death from cardiovascular causes was reported to be 8-12 times higher among women with preeclampsia and preterm delivery as compared to normotensive peers [6].

It could be suggested, therefore, that the main cause of mortality and morbidity in such cases is ischemic heart disease

Table I. Demographic and baseline biochemical measurements of patient and control groups.

	Preeclampsia (n=40)	Control (n=27)	*p*
Age (year)	33.75±7.95	36.44±10.45	0.262
Total cholesterol (mg/dl)	187.55±32.48	182.77±30.77	0.545
HDL cholesterol (mg/dl)	47.20±8.42	49.96±11.02	0.276
LDL cholesterol (mg/dl)	115.77±25.49	108.03±22.35	0.194
Triglyceride (mg/dl)	113.50±52.71	125.29±62.44	0.424
hsCRP(mg/L)	3.80±2.06	2.43±1.91	***0.007***
Creatinin(mg/dl)	0.79±0.12	0.78±0.08	0.591
Fasting Glucose(mg/dl)	93.27±6.89	95.18±7.40	0.292
ALT	21.20±11.84	20.25±7.92	0.698
Uric acid(mg/dl)	4.01±.77±	3.65±.87	0.099
Hemoglobin (g/dL)	13.59±3.81	13.39±1.27	0.762

Abbreviations:
HDL – high density lipoprotein cholesterol. **LDL** – low density lipoprotein cholesterol. **hsCRP** – high sensitive C-reactive protein.
ALT – Serum Alanine Amino Transferase. Data was presented as mean ± standard deviation.

Table II. Left ventricular systolic and diastolic function measurements.

	Preeclampsia	Control	p
Emax (cm/s)	83.52± 17.83	82.22± 16.09	0.757
Amax (cm/s)	70.45± 19.43	63.55± 11.89	0.077
E DT (ms)	209.20± 32.53	223.43± 41.39	0.219
Mitral IVRT(ms)	91.30± 15.34	88.41± 15.26	0.488
Emax/Amax ratio	1.23± 0.29	1.32± .28	0.213
Sm (cm/s)	14.31± 2.71	14.44± 2.93	0.853
Em (cm/s)	20.35± 3.97	18.70± 4.67	0.138
Am (cm/s)	15.83± 3.31	15.37± 3.31	0.579
Em/Am ratio	1.32± 0.30	1.28± .47	0.741
IVRT (ms)	98.19± 26.71	104.40± 38.16	0.468
IVCT (ms)	53. 73± 12.06	49.51± 11.46	0.153
ET (ms)	282.74± 36.55	299.88± 44.43	0.103
MPI	0.55± 0.16	0.53± 0.19	0.630
EF	69.02± 4.59	67.03± 5.57	0.133
E/e'	4.22±1.23	4.61±1.27	0.214

Abbreviations:
Sm – systolic peak velocity; **Em** – early peak velocity; **Am** – atrial peak velocity; **IVRT** – isovolumic relaxation time; **IVCT** – isovolumic contraction time; **ET** – ejection time; MPI: myocardial performance index; **EF** – left ventricular ejection fraction.; **EDT** – Mitral Emax wave deceleration time. **E/e'** – ratio of the mitral velocity to the early-diastolic velocity of the mitral annulus. Data was presented as mean ± standard deviation.

rather than preeclampsia itself [13]. In comparison with normotensive controls, there is increased arterial stiffness in preeclamptic women shortly before, during, and several months after preeclamptic pregnancies. The magnitude of this increase tends to be greater in more serious cases of preeclampsia, as well as in early-onset preeclampsia. For this reason, it might be suggested that arterial stiffness contributes to the increased risk of cardiovascular complications developing in women with a history of preeclampsia. Furthermore, arterial stiffness measurements have been proven to be of use in predicting the onset of preeclampsia [14]. According to recent reports, endothelial dysfunction might stem from abnormal placentation, insofar as the latter can cause placental ischemia and stimulate the release of placental products damaging to the maternal vascular endothelium [15, 16].

A study by Chambers et al., showed that impaired endothelial function in women with preeclampsia was not linked to maternal obesity, hypertension, metabolic disturbances associated with insulin resistance, dyslipidemia, or elevated homocysteine concentrations [16]. Instead, their results suggested was that endothelial dysfunction in preeclampsia is mediated through oxidative stress [17].

Table III. Hemodynamic. echocardiographic. aortic elastic measurement values

	Preeclampsia (n=)	Control (n=)	P
Heart rate (bpm)	76.72± 14.28	74.92± 17.24	0.656
Mean SBP (mm Hg)	116.70± 12.16	118.14± 12.41	0.639
Mean DBP (mm Hg)	74.60± 8.27	75.37± 7.32	0.690
Systolic aortic diameter (cm)	2.79± 0.42	2.80± 0.32	0.982
Diastolic aortic diameter (cm)	2.51± 0.45	2.32± 0.42	0.095
BMI (kg/m^2)	26.85± 4.44	26.20± 3.68	0.518
LA(cm)	3.11± 0.40	2.99± 0.43	0.228
LVMI (g/m^2)	79.83± 17.06	75.12± 13.42	0.215
EF(%)	69.02± 4.59	67.03± 5.57	0.133
Strain	12.24± 9.22	22.35± 15.99	***0.005***
Distensibility	6.13± 4.99	11.17± 9.68	***0.018***
Stiffness index	7.32± 6.89	3.09± 2.41	***0.001***
Elastic modulus (10^3)	7.00± 6.83	2.89± 2.11	***0.001***

Abbreviations:
SBP – systolic blood pressure; **DBP** – diastolic blood pressure; **LV** – left ventricle; **RV** – right ventricle; **LVMI** – left ventricular mass index; **EF** – left ventricular ejection fraction; **BMI** – Body-mass Index; **LA** – Left atrium diameter. Data was presented as mean ± standard deviation

Endothelial dysfunction, a major contributor to ischemic heart disease, is closely associated with nitric oxide and oxidative stress [18]. It has been shown that there is a significant level of oxidative stress even before the onset of PE, which might play a significant role in vasoconstriction, leading to endothelial dysfunction [19]. Considering that atherosclerosis can simultaneously affect the aorta and the coronary arteries, aortic stiffness and distensibility may be used to predict adverse cardiovascular events [20, 21], reduced compliance and distensibility, as well as increased stiffness independent of the BP level [22]. Accordingly, increased AoSI and AoEM or reduced AoD might be early predictors of coronary atherosclerosis, pointing to end organ damage in hypertensive individuals [23].

It has been demonstrated that severe preeclampsia is linked with the modification of the left ventricular (LV) geometry and function, diastolic as well as systolic. There are some recent reports of persistent cardiac findings detected in the echocardiography of a majority of asymptomatic women with a history of preeclampsia [24].

Echocardiography performed during the acute phase of preeclampsia has consistently revealed a number of cardiac changes like abnormal systolic function, increased systemic vascular resistance, impaired diastolic function, and LV global remodeling/hypertrophy [13–17].

According to Borghi et al., the increased LVM in preeclamptic women coincided with increased plasma levels of both, atrial and brain natriuretic peptide, which suggested a sort of latent LV dysfunction along with the structural adaptive responses. In some studies, echocardiographic assessment was repeated a few months after delivery, with the result that all researchers (except for Tyldum et al.) reported an increased prevalence of abnormal findings in women with previous preeclampsia, such as cardiac dysfunction, ventricular global remodeling/hypertrophy and hypertensive disorders. The persistence of these findings after delivery might be implying a progression towards initial organ damage [25-28].

In order to avoid the confounding effects of the left ventricular hypertrophy and left ventricular diastolic dysfunction on the study results, subjects with left ventricular hypertrophy ≥110 g/m^2 as well as PE patients with hypertension were excluded from the study. Owing to that, we were able to investigate any possible changes induced by mild PE in LV geometry.

It is considered that the ratio of peak early diastolic velocity (E) of the left ventricular inflow to peak early diastolic longitudinal velocity (e') of the mitral annulus E/e', reflects the LV filling pressure [29].

In our study, the E/e' ratio of the PE group did not differ from that of the control group. That showed that the remodeling that had developed in PE patients during the five years after delivery remained below the level that would induce a change in the LV filling pressure. However, ventricular function parameters like EF, MPI and Sm did not differ between the two groups, suggesting that the initial LV longitudinal function was preserved – a state of affairs that has recently been identified as one of the clearest signs of impaired ventricular contractility.

Paradoxically, myocardial relaxation is an energy-dependent process that leads to a rapid decrease in LV pressure following the end of contraction. As such, it is in fact a more vulnerable process than the contraction itself, and begins to reveal signs of impairment in the earliest stages of cardiovascular disorders, as well as in preeclampsia itself. A proper diastolic dysfunction was not observed in our study population, either. Nevertheless, in formerly preeclamptic women, there was a significant reduction in the E/A ratio, especially in tissue Doppler Em and Am wave peek velocity, as well as in the Em/Am ratio, while there was a significant increase in the E/e' ratio. That suggested the presence of a latent impairment in the myocardial relaxation of patients with severe PE.

Melchiorre et al., found mild to severe diastolic dysfunction in patients affected by preterm preeclampsia, and observed a year later that this dysfunction persisted. In term PE patients, however, they failed to detect a significant difference in cardiac dysfunction

Table IV. Correlation Table.

		hsCRP	STIFFINDX	STRAIN	DIST	EMOD	IVRTmax	MPI	Age	BMI	LVMI	EF	MDT	Emax/ Amax	Sm	Em/Am	E/e'
hsCRP	r	1	0.396(*)	-0.418(**)	-0.446(**)	0.365(*)	0.340(*)	0.065	-0.203	-0.259	0.028	-0.006	0.252	-0.058	-0.312(*)	-0.240	0.018
	p		0.012	0.007	0.004	0.021	0.032	0.689	0.210	0.107	0.865	0.972	0.117	0.720	0.050	0.136	0.912
STIFFINDX	r		1	-0.723(**)	-0.698(**)	0.992(**)	0.120	-0.065	-0.113	0.001	-0.018	0.095	-0.288	-0.173	-0.405(**)	-0.220	0.048
	p			<0.001	<0.001	<0.001	0.460	0.690	0.487	0.994	0.913	0.559	0.071	0.287	0.010	0.172	0.769
STRAIN	r			1	0.955(**)	-0.711(**)	-0.124	0.035	-0.017	-0.042	0.060	0.011	0.143	0.122	0.325(*)	0.331(*)	-0.084
	p				<0.001	<0.001	0.446	0.829	0.919	0.799	0.718	0.945	0.378	0.454	0.041	0.037	0.604
DIST	r				1	-0.691(**)	-0.139	0.048	0.029	0.066	0.103	-0.055	0.075	0.083	0.263	0.351(*)	-0.081
	p					<0.001	0.394	0.770	0.860	0.683	0.534	0.738	0.643	0.609	0.101	0.027	0.621
EMOD	r					1	0.101	-0.067	-0.122	0.025	-0.015	0.119	-0.289	-0.145	-0.372(*)	-0.191	0.057
	p						0.534	0.682	0.452	0.877	0.928	0.464	0.070	0.371	0.018	0.238	0.729
IVRTmax	r						1	0.281	-0.180	0.065	0.236	-0.034	0.423(**)	-0.263	-0.285	-0.225	0.128
	p							0.079	0.267	0.689	0.148	0.834	0.007	0.102	0.074	0.163	0.431
MPI	r							1	0.058	0.105	-0.078	0.100	0.187	-0.190	0.037	-0.039	0.311
	p								0.724	0.521	0.635	0.539	0.248	0.240	0.820	0.813	0.050
Age	r								1	0.104	0.126	-0.050	0.022	-0.485(**)	-0.010	-0.372(*)	0.044
	p									0.523	0.444	0.757	0.893	0.002	0.950	0.018	0.789
BMI	r									1	0.230	-0.105	-0.209	-0.002	-0.065	-0.129	0.280
	p										0.159	0.518	0.196	0.990	0.692	0.427	0.080
LVMI	r										1	-0.083	0.096	-0.221	-0.097	-0.300	0.372(*)
	p											0.617	0.563	0.176	0.558	0.063	0.020
EF	r											1	-0.060	-0.150	0.081	-0.181	0.141
	p												0.714	0.357	0.620	0.264	0.384
MDT	r												1	-0.091	-0.091	-0.107	0.057
	p													0.577	0.578	0.513	0.725
														40	40	40	40
Emax/Amax	r													1	0.184	0.398(*)	-0.042
	p														0.256	0.011	0.795
Sm	r														1	0.194	-0.171
	p															0.230	0.293
Em/Am	r															1	-0.218
	p																0.176
E/e'	r																1
	p																
	r																
	NOD(P)	0.409	0.028	0.224	0.347	0.041	0.620	0.419	0.693	0.618	0.582	0.862	0.510	0.878	0.330	0.907	0.183

Abbreviations: hsCRP: high sensitive C-reactive protein; DIST: Distensibility; EMOD: Elastic Modulus; STIFFINDX: Stiffness Index; Sm: systolic peak velocity; Em: early peak velocity; Am: atrial peak velocity; IVRT: isovolumic relaxation time; IVCT: isovolumic contraction time; ET: ejection time; MPI: myocardial performance index; BMI: Body-mass Index; LVMI: left ventricular mass index; EF: left ventricular ejection fraction.; MDT: Mitral Emax wave deceleration time. E/e': ratio of the mitral velocity to the early-diastolic velocity of the mitral annulus NOD (p): Kolmogorov- Simirnov test normality of distribution "p" values (*) represents p<0.005. (**) represents p<0.001

from the controls, independently of the degree of severity of PE. In the present study, which we performed five years after delivery on formerly preeclamptic patients, the left ventricular systolic and diastolic function findings corroborated the result of Melchiorre et al., who found that impairment of arterial stiffness values in formerly preeclamptic patients is linked to the increased hsCRP values, and showed that the subclinical atherosclerotic process developing alongside increased inflammation continues in mild PE patients [30]. It can be suggested that continuing increased atherosclerosis may help explain the increased cardiovascular mortality and morbidity that develop in PE patients in the later years of their life.

Our study suggests that the reason why diastolic function appeared largely normal in patients with PE during the check-up five years after delivery, might be a slow development of left ventricular remodeling.

The study of Scholl et al., revealed that preeclamptic women had a urinary excretion of 8 isoprostaglandin F2 that was 5 times higher than normal, what indicates oxidative damage to lipids [31]. Similarly, they had a total antioxidant power (a global measure of antioxidant status) that was 3 times lower than normal.

In our study, which excluded all patients with the risk factors of atherosclerosis and all those receiving medication, both, aortic stiffness and hsCRP values were observed to be different between the PE and control groups. Moreover, hsCRP was found to be correlated with aortic strain, distensibility, stiffness index and elastic modulus. This is evidence supporting the conclusion that inflammation plays a key role in PE patients. The finding in question may suggest that the impairment of aortic stiffness in patients with PE constitutes an early manifestation of coronary vascular involvement, as well as of coronary atherosclerosis in development. It is possible to defer the unfavorable effects of PE on the cardiovascular system by modifying other atherosclerosis risk factors.

Conclusions

In conclusion, our study showed that aortic stiffness is impaired and hsCRP are increased in patients with mild PE. These findings corroborate the important role that chronic inflammation plays in the development of endothelial dysfunction and atherosclerotic disease in PE.

We excluded subjects with confounding factors commonly encountered in normal population, including hypertension, left ventricular hypertrophy, and diabetes mellitus, morbid obesity, and current smoking, with the purpose of detecting the independent impact of PE on aortic stiffness, as well as on the ventricular systolic and diastolic function. Therefore, our study does not provide information about the effects of PE in patients with risk factors for coronary heart disease, and its results cannot be applied to the population at large.

Authors' contribution:

1. Faika Ceylan Ciftci – concept, , study design, corresponding author.
2. Ozgur Ciftc – charge of statistical analysis and manuscript draft.
3. Hakan Gull – acquisition of data.
4. Mustafa Caliskan – interpretation of data.
5. Ayla Uckuyu – revised the article critically.
6. Ebru Emel Ozcimen – the critical discussion.

Authors' statement

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