World Journal of Medical Sciences 8 (1): 56-60, 2013
ISSN 1817-3055

DOI: 10.5829/idosi.wjms.2013.8.1.71204

Performance Features of the Cardiovascular System in Middle-Aged Women with Hypertension Depending on the Estradiol Level

N.A. Koryagina, A.V. Petrishcheva, L.M. Vasilets and A.V. Tuev

E.A. Vagner Perm State Medical Academy, Perm, Russia

Abstract: Sixty four working-aged women (aged 39.34±1.98) with arterial hypertension (AH) degree I naïve to hypertensive therapy were screened. Depending on the levels of estradiol and follicle-stimulating hormone (FSH), the respondents were divided into two groups. Group 1 included 34 arterial hypertensive women with the physiological menstrual cycle and estrogen deficiency. Group 2 included 30 arterial hypertensive women with the physiological menstrual cycle and the normal levels of estradiol and FSH. The control group consisted of 20 healthy women. Duplex scanning of the common carotid artery (CCA) and transthoracic echocardiography (echoCG) with targeted investigation of left ventricular diastolic filling were performed. A decrease in elasticity of the CCA wall and a decrease in its stiffness were obtained in women with AH; these changes were more pronounced in case of estradiol deficiency. According to the echoCG data, a dysfunction manifesting itself both as abnormalities in active relaxation and as an increased myocardial stiffness of the left ventricle was resulted by the assessment of the diastolic function in women with the normal menstrual cycle and AH regardless of their hormone level (these manifestations were more pronounced in case of estrogen deficiency).

Key words: Arterial Hypertension · Estradiol · Working-aged women

INTRODUCTION

According to the results of population studies, the majority of adults (~40% in Russia) suffer from elevated arterial pressure (AP) [1]. Studying the problem of arterial hypertension (AH), one of the most common cardiovascular diseases (CVDs), arouses significant interest. The prognostic value of determining arterial stiffness in different cohorts of patients was confirmed in a number of studies. The list of arterial disorders in patients with AH also includes arterial adjustment accompanied by the disturbance in damping function of arteries with the changes in left ventricular afterload and coronary perfusion. Men and women have a number of common risk factors (RFs) of CVDs. However, women have an additional risk factor: a decline in ovarian function and development of a deficiency of female sex hormones (primarily, estrogens) in perimenopause period [2-4]. Certain progress in studying the structural-functional rearrangement of the cardiovascular system in women with AH during various periods of their lives has been achieved. The question concerning the pathogenetic association between the estradiol level and the pattern of structural-functional changes in the cardiovascular system in women during the late reproductive period remains poorly studied [5, 6]. This question is of practical interest and allows one to draft recommendations for improving the quality of examination of working-age women before they reach menopause in order to prevent the early development of cardiovascular complications.

Objectives: investigation on the clinical manifestations due to associations between the changes in the levels of estradiol and follicle-stimulating hormone (FSH) and the structural rearrangement of the cardiovascular system in working-aged women during the late reproductive period.

MATERIALS AND METHODS

Cross-sectional study was carried out in a private hospital. Female patients attending gynecologic clinic were included into the study. Sixty four working-aged

Corresponding Author: Koryagina, Perm State Medical Academy, Dean's Office of the Department of Higher Nursing Education, ul. Petropavlovskaya 26, Perm, 614000 Russia.

women (aged 36-45) in the late reproductive period with AH degree I naïve to hypotensive therapy were examined. The AH diagnosis was verified in compliance with the Russian Guidelines for Prevention, Diagnosis and Treatment of Arterial Hypertension [7]. The levels of estradiol and follicle-stimulating hormone (FSH) were determined in each woman. These measurements were performed three times in order to verify the absolute character of hypoestrogenia during the folliculin phase of the menstrual cycle (the mean values).

Depending on the levels of estradiol and FSH, the respondents with AH were divided into three groups. Group 1 included 34 women with AH (median age 39.11±4.3 years), physiological menstrual cycle and estrogen deficiency (reduced estradiol level and increased FSH level). Group 2 consisted of 30 women with AH degree I (median age 39.14 ± 2.23 years), physiological menstrual cycle and normal levels of estradiol and FSH. The general characteristics of female patients with AH were listed in Table 1. The groups are comparable in terms of the age, severity of AH, duration of AH and body mass index. Identical therapy (angiotensin II inhibitors, diuretics) was prescribed to the patients within the first week following the screening.

The following exclusion criteria were applied: secondary AH; ischemic heart disease, diabetes mellitus, cardiac rhythm disorders, dyslipidemia, clinical manifestations of the climacteric syndrome, hemodynamically significant stenosis of the common carotid arteries (CCA), disability.

The control group included 20 healthy women attending the gynecologic outpatient clinic (median age 38.45 ± 4.12) with the normal levels of estradiol and FSH, with neither AH nor chronic diseases affecting the intracardiac hemodynamics.

Duplex scanning of the CCA was carried out on a LOGIQ P5 Expert ultrasonic diagnostic apparatus (General Electric, USA, 2010) in order to assess the structural-functional state of the vascular bed in all female patients in the late reproductive period. The mean value (half of the sum of systolic and diastolic diameters) was used as a reference. The intima media thickness (IMT) was studied. The distensibility coefficient (DC) and the stiffness index (SI) were used to assess the elasticity of the CCA. DC was calculated using the formula: DC = 2xAD/D PAP/D{1 G* kPa}, where D is the arterial diameter; AD is the change in the arterial diameter during the cardiac cycle; and PAP is the pulse arterial pressure [8]. Stiffness index was calculated using the formula: SI = log (SAP/DAP) // (AD/D), where D is the arterial diameter; AD is the change in the arterial diameter during the cardiac cycle [9]. The peak systolic blood flow velocity (cm/s) and the resistance index (RI) (units) were analyzed based on the hemodynamic parameters of intravascular blood flow.

Echocardiography (echoCG) was performed in the female patients in order to determine the features of hemodynamic parameters. Transthoracic echoCG was performed using a LOGIQ P5 Expert ultrasonic apparatus (General Electric, USA, 2010) with a 3.75 MHz-frequency sensor according to the conventional procedure [10] recommended by the American Society of Echocardiography [11].

The targeted investigation of left ventricular (LV) diastolic filling was performed to determine the following parameters: the peak velocity of left ventricular early diastolic filling (velocity E), (m/s); the peak velocity of late diastolic filling (velocity A), (m/s); the integral of the peak velocity of early diastolic filling (integral E), (m); the integral of the peak velocity of late diastolic filling (integral A), (m); the total transmitral flow integral (total integral), (units); the ratio between the integral of LV late diastolic filling and the integral of LV early diastolic filling (integral A/E), (units); the ratio between the integral of LV early diastolic filling and the total transmitral flow integral (integral E/total integral), (units); the ratio between the integral of LV late diastolic filling and the total transmitral flow integral (integral A/total integral), (units); the isovolumic relaxation time (time between the first large oscillation of the second heart sound and the onset of the transmitral flow)- (IVRT), (ms)). The indices of active relaxation (AR) and left ventricular stiffness were analyzed separately in order to assess the degree of distortion of diastolic filling. The AR phase was assessed using the following parameters: the peak velocity of left ventricular early diastolic filling (velocity E), (m/s); the integral of the peak velocity of early diastolic filling (integral E), (m); the isovolumic relaxation time (IVRT), (ms) [12].

Statistical and mathematical processing of the results was performed using Statistica 6.2 software package.

RESULTS AND DISCUSSION

The data obtained by analyzing the parameters of the structural-functional state of the vascular bed in female patients with AH depending on the hormone level were listed in Table 2.

The comparative analysis of the carotid artery diameter in the clinical groups under study as compared to those of healthy women was showed in Table 2.

Table 1: General characteristics of female patients with AH.

Indices	Group 1 (*n*=34)	Group 2 (*n*=30)	*p*
Age, years	39.11±4.3	39.14±2.23	0.91
Estradiol level, pg/ml	0.32±0.06	0.59±0.087	0.003
FSH level, mU/ml	13.37±1.35	6.54±0.34	0.004
SAP_{mean}, mm Hg	142.1±14.88	143.2±13.78	0.78
DAP_{mean}, mm Hg	87.21±9.13	87.9+13.4	0.81
Duration of AH, years	4.2±1.5	3.8±1.7	0.76
Body mass index, kg/m^2	28.64 ±2.5	26.34±2.8	0.21

Table 2: Indices of the structural-functional state of the vascular bed.

Indices	Group 1 (n=34)	Group 2 (n=30)	Control groups (n = 20)	*p* 1-2	*p* 1-3	*p* 2-3
CCA diameter (mm)	7.12±0.9	6.2 ±0.34	5.75±0.78	0.03	0.0012	0.00013
IMT (units)	0.78±0.5	0.62±0.4	0.49±0.19	0.04	0.008	0.03
Velocity, cm/s	72.9±6.4	79.8±10.8	96.4±16.2	0.0061	0.0034	0.047
RI, (units)	0.85±0.021	0.76±0.031	0.72±0.024	0.064	0.0031	0.071
DC, (units)	32.1 ±10.7	39.1 ±8.4	41.3±10.5	0.05	0.0023	0.007
SI, (units)	7.3± 0.4	6.8 ± 0.8	6.5±0.7	0.09	0.04	0.05

There is an increase in the mean carotid artery diameter (mostly in female patients with AH and estrogen deficiency). The velocity of blood circulation in CCA was lower among the female patients with AH and hypoestrogenia. The resistance index was higher in group 1 women with AH as compared to those for the female patients in group 2 and the control group. The elastic properties of the carotid artery wall decreased from 41.3±10.8 × U^{-3}/ kPa in female patients with AH and the normal estradiol level to 36.4±10.8 × U^{-3}/ kPa (*p*=0.034) in women with AH and reduced estradiol level. The stiffness index both in AH patients with and without estrogen deficiency appeared to be higher than that in the control group.

The obtained data demonstrated the elasticity of the common carotid artery wall decreases, while its stiffness increases in women with AH (special attention should be paid to the arterial hypertensive female patients with the decreased estradiol level and increased FSH level).

The diastole is a complex hemodynamic process controlled by a number of factors, including the relaxation and stiffness of left ventricular myocardium, the state of systolic function, atrial size and left ventricular end-diastolic pressure [13]. The changes in any of these factors result in an increase in resistance of left ventricular filling during diastole (i.e., in diastolic dysfunction) [14]. In order to study the diastolic function of the LV, we analyzed the parameters allowing one to assess the active relaxation of left cardiac compartments and myocardial rigidity. The changes attesting to the disruption of active relaxation of the LV (Table 3) were observed in all groups. According to the European Guidelines for EchoCG (2008), the following parameters are significant for the assessment of the diastolic function of the left ventricle: the velocity of left ventricular early diastolic filling (E), which indirectly attests to the pressure differential in the left ventricle and IVRT showing the degree of relaxation of the left ventricular wall.

The analysis demonstrated that the phase of active relaxation was disturbed in female patients with AH regardless of the levels of estradiol and FSH. This fact was supported by a decrease in the velocity of early diastolic filling E as compared to that in the control group (from 0.82±0.11 in the control group to 0.68±0.09 in female patients with AH and the normal estradiol level and to 0.66±0.081 in female patients with estrogen deficiency) and a decrease in the integral of the peak velocity of early left ventricular filling (whose values both in female patients with the normal estradiol level and in those with reduced estradiol level and increased FSH level reliably decreased as compared to the control group).

The decrease in the aforementioned indices in the analyzed groups was accompanied by a significant increase in the isovolumic relaxation time (from 65.31±4.56 ms in the control group to 102.6±7.8 ms in female patients with the normal levels of estradiol and FSH and to 106.2±6.71 ms in female patients with reduced estradiol level and elevated FSH level, respectively). The changes in women with AH were accompanied by a decrease in the ratio between the integral of the velocity of early diastolic filling E and the total transmitral flow velocity integral:

Table 3:State of the indices of active relaxation of left ventricular myocardium.

Indices	Group 1 (*n*=34)	Group 2 (*n*=30)	Control group (*n*=20)	*p* 1-2	*p* 1-3	*p* 2-3
Velocity E, (m/s)	0.66±0.81	0.68±0.09	0.82±0.11	0.08	0.0003	0.002
Integral E (m)	0.09±0.021	0.12+0.02	0.15±0.04	0.03	0.04	0.02
Integral E/total flow integral (units)	0.53±0.04	0.55±0.09	0.64±0.06	0.12	0.003	0.04
IVRT (ms)	106.2±6.71	102.6±7.8	65.31±4.56	0.03	0.0007	0.001

Table 4:Stiffness indices of left ventricular myocardium.

Indices	Group 1 (n=34)	Group 2 (n=30)	Control group (n=20)	*p* 1-2	*p* 1-3	*p* 2-3
Velocity A (m/s)	0.69±0.17	0.63±0.13	0.61 ±0.13	0.09	0.12	0.78
Integral A (m)	0.081±0.02	0.091±0.01	0.082±0.01	0.04	0.08	0.81
Integral A /integral E (units)	0.88±0.31	0.76±0.67	0.70±0.18	0.04	0.0013	0.08
Integral A/total flow integral (units)	0.45±0.04	0.47±0.09	0.39±0.07	0.003	0.004	0.004
Flow deceleration time E	123.3±12.8	147.3±23.97	178.76±19.21	0.001	0.0003	0.002
EDP						
(mm Hg)	16.4±5.4	14.21±3.67	10.87±3.12	0.04	0.0001	0.006
EDWS (dyn/cm^2)	21.2±4.01	14.22±5.67	10.11±3.45	0.0013	0.001	0.007

from 0.64±0.06 in the control group to 0.55±0.09 in female patients with AH and the normal levels of estradiol and FSH and to 0.53±0.04 in the group of women with reduced estradiol level. The data demonstrated that regardless of the estradiol and FSH levels, the active relaxation of left ventricular myocardium was disturbed in female patients with AH. The IVRT values in female patients with reduced estradiol level and elevated FSH level differed from those in women with the normal levels of these hormones (106.2±6.71 and 102.6±7.8, respectively). This fact attests to the diastolic dysfunction and more pronounced abnormalities in active relaxation of the left ventricle (rigid diastolic dysfunction).

The basic and derived values characterizing the stiffness of the left ventricular myocardium in patients with different levels of estradiol and FSH (Table 4) significantly differed from those in the control group and attested to the reduced elasticity of the left ventricular myocardium and its increased stiffness in both groups of female patients with AH.

The deceleration time E is the index representing the elasticity of the left ventricular myocardium. It decreased from 178.76±19.21 in healthy women to 147.3±23.97 in female patients with the normal levels of estradiol and FSH and to 123.3±12.8 in female patients with estrogen deficiency. The ratio between the integral A and the total transmitral flow integral, which represented active contribution of the atria to left ventricular filling, reliably increased both in female patients with the normal levels of estradiol and FSH and in women with estrogen deficiency as compared to the control group (0.47±0.09 in women with the normal estradiol and FSH levels, 0.45±0.04 in women with hypoestrogenia and 0.39±0.07 in the control group, respectively; $p<0.05$).

The changes in the end-diastolic wall stress (EDWS) of the left ventricle were observed. When analyzing the indices of left ventricular myocardium stiffness in different groups of female patients with AH, women with the reduced estradiol level and elevated FSH level were found to have significantly higher values of integral A, the integral A/integral E ratio, EDWS with low deceleration time E, which shows higher degree of left ventricular myocardium stiffness in this group as compared to that in arterial hypertensive female patients without estrogen deficiency.

Thus, the data of the comparative analysis of the diastolic function in female patients with AH, regardless of their hormone level, attest to the fact that they have a dysfunction associated either with abnormalities in active relaxation or with increased left ventricular myocardium stiffness. The dysfunction manifests itself to a higher extent in women with estradiol deficiency.

CONCLUSIONS

- Duplex scanning of the common carotid arteries in women in the late reproductive period with AH showed an increase in the CCA lumen diameter and a decrease in blood flow velocity in carotid arteries, which was more pronounced in women with estrogen deficiency. These facts attest to more significant changes in the vascular wall as compared to those observed in arterial hypertensive female patients with the normal hormonal background.

- The diastolic dysfunction with abnormalities in relaxation phase and increased stiffness of the myocardium of left cardiac compartments in arterial hypertensive women with the normal estradiol level is less pronounced as compared to that in women with hypoestrogenia.
- When screening women with AH (aged 36-45), special attention should be paid to the reduced estradiol level and elevated FSH level as the risk factors for the development of arterial hypertension.

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