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INFLUENCE OF SEX, AGE AND DEGREE OF ARTERIAL HYPERTENSION ON THE VASCULAR WALL STIFFNESS

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The purpose of the study was to investigate the correlations between pulse wave velocity and the blood pressure degree, age and gender in patients with different degrees of arterial hypertension. 86 people were included were included into the clinical observation at the Cardiology Clinic of the Military Medical Clinical Center of the Southern Region. Patients were randomized into 2 groups – group 1 was consisted out of 71 patients with various degrees of arterial hypertension, group 2 was consisted out of 15 conditionally healthy individuals. Pulse wave velocity was measured in all patients. Authors studied in details the influence of age, gender and blood pressure level on vascular stiffness formation. The presence of a certain marker of the vascular bed functioning was shown and studied with correlative relations with the named above factors that is extremely important because one could assume the risk of a vascular catastrophe approaching according to its absolute value change. The conclusion made that age is one of the significant factors determining the vascular stiffness formation. The formation of vascular stiffness characterized also by gender characteristics. The arterial rigidity stiffness severity shown to be increased as the degree of arterial hypertension increases; it correlates with systolic blood pressure. Pulse wave velocity index determination is a sensitive marker of vascular remodeling in premorbid hypertensive conditions and in young people.

Key words: arterial hypertension, vascular wall stiffness, rigidity, age, gender, blood pressure, pulse wave velocity

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ВПЛИВ СТАТІ, ВІКУ ТА СТУПЕНЯ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ НА ЖОРСТКІСТЬ СУДИННОЇ СТІНКИ

Метою дослідження було вивчення кореляції між швидкістю пульсової хвилі та ступенем артеріального тиску, віком і статтю у хворих з різними ступенями артеріальної гіпертензії. Для клінічного спостереження у кардіологічній клініці Військово-медичного клінічного центру Південного регіону були задіяні 86 осіб. Пацієнти були рандомізовані на 2 групи – 1 групу склав 71 хворий з різним ступенем артеріальної гіпертензії, 2 групу склали 15 умовно здорових осіб. У всіх пацієнтів вимірювали швидкість пульсової хвилі. Автори детально вивчили вплив віку, статі та рівня артеріального тиску на формування жорсткості судин. Показано наявність маркера функціонування судинного русла та досліджено його кореляційні взаємовідносини із вказаними чинниками, що є надзвичайно важливим, оскільки за зміною його абсолютної величини можливо припустити ризик виникнення судинної катастрофи. Зроблено висновок, що вік є одним із суттєвих чинників, що визначають формування жорсткості судин, яке у свою чергу характеризується також статевими особливостями. Показано, що ригідність стінок судин зростає зі збільшенням ступеня артеріальної гіпертензії; цей маркер корелює з величиною систолічного артеріального тиску. Визначення індексу швидкості пульсової хвилі є чутливим маркером ремоделювання судин при преморбідних гіпертонічних станах і в осіб молодого віку.

Ключові слова: артеріальна гіпертензія, жорсткість судинної стінки, ригідність, вік, стать, артеріальний тиск, швидкість пульсової хвилі

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The characteristics of pulse fluctuations have been used to diagnose both vascular and cardiac diseases. One of the pulse wave characteristics – velocity of its movement through the arterial vessels – remains a valuable indicator for arterial wall stiffness degree evaluation [6, 14].

Large-diameter arteries elastic properties decrease as the result of their age-dependent or pathological thickness in atherosclerosis, coronary heart disease, systemic connective tissue diseases and other vascular diseases is accompanied by both maximal systolic blood pressure (SBPmax) and pulse pressure (PP) amplitude increase and is manifested by pulse wave velocity (PWV) acceleration [13]. Named indexes increase creates a risk of target organs vessels damage [4].

The pulse wave (PV) occurs as a result of blood pressure drop during left ventricle systole and diastole gives an extensive information about the cardiac work, hemodynamic parameters changes, the cardiac valvular apparatus condition, the compression chamber vascular walls elasticity (maximal systolic blood pressure index) and other cardiovascular system indexes [6].

PWV acceleration is considered to be as one of the big arteries walls rigidity and cardiovascular system diseases risk of development objective diagnostic sign. While both SBPmax and PP increase is considered to be as microcirculatory vessels damage predictive factors [12].

The mechanisms of arterial wall stiffness increasing remains poorly understood even though both PWV in big arteries and pulse wave various parameters measurement are widely used to evaluate their walls stiffness and vascular diseases early diagnosis [12].

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The leading mechanisms of vascular stiffness increase additionally to vascular walls atherosclerotic damage include different types of collagen accumulation inside with a simultaneous elastin level decrease, these proteins ration changes [13] as well as collagen glycosylation [14].

Collagen accumulation inside the vascular wall mechanisms decoding could play an important role in the treatment efficacy increase aimed at vascular stiffness reducing in the course of arterial hypertension (AH), diabetes mellitus and their complications prevention [8, 10, 14, 15]. Small arterial vessels PWV measurement could also be used to determine the state of their walls, especially their thickening. However, due to their branching, variable shape and complex vascular networks, these measurements are more difficult to perform than in big vessels, and the few data of these measurements in the literature as well as their interpretation remain controversial [7].

Arterial stiffness is considered to be a key parameter of early "vascular aging" concept [10] according to which "vascular aging" being the most important risk factor of cardiovascular diseases development is determined by intrauterine development program on which the other risk factors are superimposed in the future.

Aortic PWV evaluated using the sensors carotid-femoral location is currently the "gold standard" for arterial stiffness (rigidity) measuring and this test should be recommended for cardiovascular risk assessing [1, 15].

Thus, many experts accent that arterial stiffness index increase (i.e., PWV) is not only the cardiovascular complications independent predictor but also the most reliable prognostic marker among other risk factors [1, 6].

The purpose of the study was to investigate the correlations between pulse wave velocity and the blood pressure degree, age and gender in patients with different degrees of arterial hypertension.

Materials and methods. 86 persons were included were included into the clinical observation at the Cardiology Clinic of the Military Medical Clinical Center of the Southern Region (Odesa). These patients were randomized into 2 groups of observation. The group 1 was consisted out of 71 patients with various degrees of arterial hypertension (AH), the group 2 (control group) was consisted out of 15 conditionally healthy individuals taken into observations to verify the PWV index.

The following criteria were used for the patient's inclusion into clinical observations: the patient's informed consent, various degrees of AH, namely: borderline arterial hypertension (BAH), AH of the 1st degree and AH of the 2nd degree. Exclusion criteria we used were the following: age over 59 years, AH of the 3rd degree, cardiac rhythm and intracardiac conduction disturbances, any form of atrial fibrillation, rheumatological diseases with vascular damage, acute coronary syndrome, diabetes mellitus type 1 or 2, internal organs chronic diseases in the stage of subcompensation and decompensation, oncological diseases.

Age of the patients ranged from 18 to 59 years; the average index was equal to 39.6±12.5 years. According to WHO age-dependent classification the patients of the group 1 were divided into two groups: 41 patients (57.7 %) were in the "young" age – 18–44 years, 30 patients (42.3 %) were in the "middle: age – 45–59 years.

The group 1 patients were divided additionally by gender to investigate its influence on PWV: therefore50 men and 21 women were included into survey.

To investigate the AH index influence on vascular stiffness the group 1 patients were divided also according the various degrees of AH on the following three subgroups: 14 patients with BAH (19.7 %) consisted the subgroup 1, 27 patients with the 1st degree of AH (38.0 %) consisted the subgroup 2 and 30 patients with the 2nd degree of AH (42.3 %) consisted the subgroup 3.

PWV was measured using a specially designed original device using generally accepted carotid-femoral technique [2]. Mechanosensitive sensors were applied on the skin in the area of both the carotid (the 1st sensor) and femoral (the 2nd sensor) arteries projection with two pulse waves simultaneous recording. PWV index was calculated using the raw data obtained with the help of the formula L/t where "L" is the distance between the sensors and "t" is the pulse wave delay time.

The results presented as M±σ where M is the arithmetic mean and σ is the standard deviation. The groups were tested for the Gaussian distribution using the Shapiro-Wilk test. Mann-Whitney U-test was calculated for the significance of differences quantitative characteristics between groups estimation. We calculated the Spearman rank correlation coefficient to study the correlations between age, gender, AH degrees and PWV – strong relationship we considered at r=0.7–0.99, middle relationship at r=0.3–0.69 and a weak relationship at r<0.3. All the statistical calculations were made using the program "Statistica 10.0".

The minimal statistical probability was determined at $p<0.05$.

Results of the study and their discussion. PWV index in relatively young AH patients approached to its "upper" borders and was equal to 9.5±1.5 m/s. The correlation PWV vs age was "strong" and significant (r=0.802, p<0.001, Table 1).

Table 1

PWV in young and middle age patients with AH

Index	Patients 18–59 years	Group 118–44 years	Group 245–59 years
Average age	39.6±12.5	30.9±8.6	51.5±4.4
Gender	51/20	34/7	16/14
Systolic BP, Hg.mm	153.9±14.6	143.6±8.8	168.0±6.8***
Diastolic BP, Hg.mm	96.9±8.3	91.5±6.5	104.3±3.5***
PWV, m/s	9.5±1.5	8.60±1.15	10.7±1.1***
Spearman rank, r	0.802	0.782	0.124

Note: *** – $p<0.001$ – the significant differences of the investigated indexes compared with those in patients of group 1 (Mann-Whitney U-test).

The data obtained showed that PWV index in relatively young (18–44 years) AH patients did not exceed the normal values (up to 10 m/s) and was equal to 8.6±1.15 m/s. In group 2 AH patients this index was increased on 24.4 % pertaining the same index in group 1 AH patients thus significantly exceeded its standard values ($p<0.001$). Important to stress PWV index increasing was registered in 5 out of 41 (12 %) patients of group 1 whereas in group 2 with the older patients its increase was registered in 20 out of 30 (66.7 %) patients. Our results detected "high" correlation between PWV and the age of wide patients' contingent from 18 to 60 years ($r=0.802$) that is in correspondence with other authors opinion and indicate that age is one of the leading factor influencing the arterial stiffness formation.

We calculated also the correlative indexes of PWV vs different age groups. The Spearman correlation coefficient in the above table in relatively young group 1 was equal to 0.782 ($p<0.05$) which indicated a "high" and significant dependence between age and vascular wall rigidity. We failed to register such a statistical correlation in group 2 patients – the relationship expression was concluded as "weak" and equal to 0.124 ($p>0.05$). This correlation weakening becomes even more important taking into consideration the fact of both systolic and diastolic blood pressure significant increase in group 2 patients vs the same indexes in group 1 patients (in both cases $p<0.001$).

We investigated the gender influence on vascular vessels rigidity also. With this aim our AH groups 1 and 2 were additionally divided on male ($n=50$) and female ($n=21$) subgroups for better PWV index determination and correlations calculation. The average age of men was 36.9±12.9 years and women 42.9±8.7 years which indicates these groups identity by age index ($p=0.70$). our registrations showed that PWV indexes in men were equal to 9.4±1.7 m/s and in women – 9.8±1.2 m/s, i.e. they also demonstrate statistical identity ($p=0.29$).

A more thorough analysis allowed to reveal the presence of PWV tendency to slight increase in due to simple number of women with PWV >10 m/s (9 out of 21 women, 42.9 %) while only 19 out of 50 male (38.0 %) demonstrated the same increase. This idea proved by the fact that PWV index equal to 6-7 m/s was registered in 3 men while there were no women with such PWV index at all.

It should also be taken into account that women average age tended to increase compared with the same in men ($p=0.70$). All this does not contradict the data of other authors presented the results of a lower degree of vascular rigidity in women and is confirmed by our results on the PWV correlation dependence vs gender study. Spearman rank in male patients with AH equal to $r=0.911$, in female group of AH patients equal to $r=0.335$ which indicates a "strong" relationship between rigidity and males and a "weak" one in females.

Taking into account the already presented above data concerning the correlations peculiarities in patients of different ages we followed our clinical observations to evaluate the gender influence on the investigated indexes. Our results shows that all the studied groups/subgroups were comparable in terms of age and levels of systolic and diastolic pressure ($p>0.05$, Table 2).

Spearman rank test in groups N5–8 is given as ratio "Syst BP vs PWV" in the numerator and as ratio "Diast BP vs PWV" in the denominator

A comparative analysis of the gender vs PWV index correlation revealed a "strong" relationship ($r=0.865$) in men aged 18–44 years and a "weak" relationship ($r=0.107$) in women of the same age. The severity of this correlation in the older age group (45–59 years) of men and women was at the "weak" level ($r=0.082$ and $r=0.052$, respectively).

The data obtained indicate a significantly smaller relationship PWV vs age in women compared with the same in men as well as a decrease of rigidity dependence with increasing age in both male and female patients' population

PWV index dynamics also showed greater women blood vessels elasticity with age increasing: with its relatively identical values at the "young" age of both sexes (8.5±1.15 vs 9.1±1.1, respectively,

p>0.05) one could observe the tendency to PWV increase in the "middle" age group where female PWV index increased till 10.1±1.03 m/s (p=0.093) while the same female index increase (11.3±0.8 m/s) was more statistically evident (p<0.001). This result indicates significant difference (p=0.006) of PWV greater increase with age in men compared to women.

Table 2

PWV in patients with AH depending on gender and AH degree

N	Groups/Index	Average age	Systolic BP, g.mm	Diastolic BP g.mm	PWV, m/s	Spearman rank, r
1	Males Group N1 18–44 years	29.90±8.95	143.1±9.3	90.97±6.9	8.50±1.15	0.865
2	Males Group N2 45–59 years	51.9±4.5	170.0±6.6	105.1±3.3	11.3±0.8	0.082
3	Females Group N1 18–44 years	35.4±4.6	145.9±5.9	94.1±2.9	9.1±1.1	0.107
4	Females Group N2 45–59 years	51.0±4.5	165.9±6.7	103.3±3.7	10.1±1.0	0.052
	$P_{intergroup}$	P_{1-3}=0.18 P_{2-4}=0.60	P_{1-3}=0.30 P_{2-4}=0.60	P_{1-3}=0.16 P_{2-4}=0.24	P_{1-3}=0.21 P_{2-4}=0.006 P_{1-2}=0.000 P_{3-4}=0.093	
5	Group N1 Healthy, n=15	23.40±1.96	118.5±5.0	75.9±8.0	6.7±1.4	r=0.21 r=0.11
6	Group N2 BAH, n=14	20.60±1.79	134.6±1.8	84.3±1.8	7.5±0.5 P_{5-6}=0.03	r=0.50 r=0.43
7	Group N3 AH 1st degree, n=27	36.5±5.4	147.5±5.9	94.6±3.2	9.1±0.9 P_{5-7}<0.001	r=0.76 r=0.52
8	Group N4 AH 2nd degree, n=30	51.20±4.98	168.7±6.2	104.8±3.3	10.8±1.1 P_{5-8}<0.001	r=0.82 r=0.58

Notes: the statistical probability calculated between the four subgroups using the Mann-Whitney U-test.

There were 4 out of 16 men (25.0 %) at the age of 45–59 years with PWV >12 m/s that gave 3.5 times more prevalence compared with the same index increasing in women (1 out of 14 women, 7.1 %). Totally, there were 5 out of 30 persons (16.7 %) with PWV index increase in the older group of the patients. These results indicate a slower and less pronounced decrease in blood vessels elastic properties in women.

It was interesting to study the effect of the blood pressure level on stiffness formation. It's important that the survey included not only patients with the 1st and the 2nd degrees of AH but also patients with BAH which is of particular importance from the point of view of stiffness changes in premorbid conditions. As usual all groups were comparable by sex, however, the average age in each of the groups increased as the degree of AH increased.

The PWV index increased significantly to 7.5±0.5 m/s in subjects even with normal but high bordering level of blood pressure (BAH) and the difference was significant (p=0.03). This is especially important considering that the average age of BAH persons was younger (20.6±1.79) vs the same of healthy people (23.4±1.96). The PWV index in patients with AH of the 1st degree has already approached the upper limit of its standard values (9.1±0.9 m/s) and it has exceeded them (10.8±1.1 m/s) in patients with AH of the 2nd degree – the difference in all groups was highly significant (p<0.001).

Correlative relations PWV vs blood pressure in each group's calculation showed that this relation in the control group was considered as "weak" (r=0.21) and not-significant (p>0.05) while in all other groups (patients with BAH, AH of the 1st and the 2nd degrees) this relation expression was determined as "strong" and "medium" (r=0.43-0.76). One should notice that correlative relation PWV vs systolic BP started to be increased ("middle") even with BAH (r=0.50, p=0.07) reaching maximal expression ("strong") in patients with AH of the 1st degree (r=0.76, p<0.001) and being slightly falling ("middle") in patients with AH of the 2nd degree (r=0.82, p=0.003).

This indicates that systolic BP value directly determined rigidity development, and higher is the systolic BP index the more pronounced is rigidity. It is especially necessary to emphasize that such a direct relationship formation was registered in conditions of AH absence in healthy individuals till its "middle" level in BAH while AH expressed clinical manifestations were not yet observed.

Controversially, analyzing correlative relations PWV vs diastolic BP one should express its ("strong", p≥0.7) absence in all of the examined groups. However, this correlative relation "middle" expression has tendency to be increased in the following row: BAH (r=0.43) → AH of the 1st degree (r=0.52) AH of the 2nd degree (r=0.58). These results allowed to conclude that there is a direct relationship between the BP level and rigidity and this relationship more expressed in systolic BP pertaining the diastolic BP.

Anticipating the initial elements of the discussion, we note that we tried to investigate the correlative relationship between the degree of vascular stiffness and a number of factors, such as the age of patients with AH, the severity of hypertension itself, gender differences and the degree of blood pressure change during the systolic and diastolic periods of cardiac muscle contraction. We were guided by convincing evidence that vascular stiffness increase during physiological aging occurs due to collagen and elastin imbalance, mediacalcinosis and impaired vasodilation [6]. The intima-media complex thickness was shown to triples [13] in the range of 20–90 years, from the other side, the biological age is known not always correspond to the vascular age. This led to the proposal to evaluate precisely the vascular age for a more accurate structural and functional changes in the body assessment and, and most importantly, to predict adverse outcomes [8].

To discuss the results obtained one should take into consideration the following four aspects. Firstly, the fundamental vascular stiffness importance is due to these criteria determine direct bloodflow to organs and tissues which is vitally important in an organism. Normal bloodflow in conditions of adequate arterial BP is known to be carried out by both myogenic and endothelial mechanisms, mainly arterioles and does not require vascular walls smooth muscle layer excessive contraction. The signaling pathways and smooth muscle mechanisms of smooth myocytes hypertrophy activated in case of long-term pulsatile blood systolic and pulse pressure increase that leads to their remodeling and lumen decrease [4]. These intravascular events and regulatory disturbances create an additional resistance to bloodflow that contributes to AH appearance and progression together with complications development (microcirculatory vessels density decrease, development of ischemia and cells of vital target organs hypoxia [11].

Thus, the presence of a certain marker of the vascular bed functioning is extremely important because one could assume the risk of a vascular catastrophe approaching according to its absolute value change. In other words, we are addressing the issue of early diagnosis of both hypertension and the complications caused by this pathological condition. From this point of view the data obtained indicate that stiffness of the walls of blood vessels increases already in the early stages of the AH development - in patients with BAH. Vascular walls stiffness has direct correlation with the systolic BP value, it progresses further as the AH degree increases and often precedes the first clinical symptoms appearance and manifestation. Therefore, we conclude that this index can become a reliable marker of premorbidity.

The second item that we think is important also. We showed the age dependency in PWV index. In our opinion, a more pronounced PWV dependence in young people may be because other mechanisms are involved into vascular wall rigidity formation/increase (endothelial dysfunction, redox imbalance, atherosclerosis, inflammatory processes, expressed AH, etc.) in patients aged 45–59 years.

The experts [6] recommended to use PWV index >12 m/s as a criterion for AH inducing aorta and target organs damage that's why we decided to study the distribution of patients with PWV of such an index in all investigated groups. Our data failed to reveal single episode of PWV index exceeding 12 m/s in both men and women aging 18–44 years.

Important to emphasize that vascular wall rigidity degree is not so much dependent especially on age but on age-related pathological conditions that directly affect muscular layer of the vascular wall - inflammation, hypoxia and oxidative stress due to metabolic processes disorders are the main factors that increase the degree of vascular walls smooth muscle layer functional activity impairment [1, 7, 15]. As for us, it is important not so much to have a convenient prognostic tool for the vascular stiffness formation but to understand the mechanisms of its occurrence, intensification and possible variability.

From the third aspect, many studies in medicine are providing now taking into account gender differences. The Framingham Heart Study was the first to show significant differences between men and women not only in disease course but also in medical correction [5] that was subsequently confirmed by other authors [9]. We found only two works, which present the gender-related results of vascular stiffness studies [3]. Our domestic scientists did not publish any works devoted to this topic. In this regard, it seems important to us the revealed vascular stiffness development gender-dependency. Interesting that vascular elasticity decrease is slower and less significant in women compared to men that could explained, in our opinion, by estrogens protective effect on the vascular wall.

And the last one, we were intriguing in some weakening of the correlation PWV vs AH severity. Being absolutely illogical this fact might be explained, in our opinion, by the older age group of patients with AH of the 2nd degree. Important to understand that other mechanisms are included into the vascular wall rigidity increase in the older category of patients. In addition, it should be taken into account that a comorbid pathology is often found in patients with hypertension after 50 years of age that can make its own "contribution" to the blood vessels elastic properties change. As a result, our data indicate that vascular stiffness increase is formed already in the early stages of AH (BAH) which further progresses as the AH

severity increases and often precedes the first clinical symptoms appearance. Therefore, the PWV criterion we study can be used as a reliable marker of AH premorbidity.

Conclusions

1. Age is one of the significant factors determining the vascular stiffness formation, and this dependence in patients of "young" age (18–44 years) was more pronounced than in patients of "middle age" (45–59 years).

2. The formation of vascular stiffness is characterized by gender characteristics: women have a slower and less pronounced decrease in the vascular elastic properties compared to the same in men.

3. The arterial stiffness severity increases as the degree of arterial hypertension increases. It correlates with systolic blood pressure. The significant PWV increase registered even at normal high blood pressure values.

4. PWV index increase is a rather sensitive marker of vascular remodeling in premorbid conditions and in young people.

Prospects for furthers researches include a subsequent comprehensive clinical observation of larger groups of patients with arterial hypertension to determine the detailed age, gender, blood systolic and diastolic pressures differences influence of the degree of vascular wall stiffness changes. An exact diapason of PWV index use for vascular tone and vascular wall rigidity evaluation with diagnostic aim should be a result of these clinical studies.

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