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THE INVESTIGATION OF VASCULAR STIFFNESS IN PATIENTS DEPENDING ON DIFFERENT DEGREES OF ARTERIAL HYPERTENSION

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The purpose of the study was to investigate the dependence of vascular stiffness on blood pressure level in patients with arterial hypertension. 90 people were included into the clinical observation. These patients were randomized into 2 groups. The group 1 was consisted of 15 healthy individuals The group 2 was consisted of 75 patients with arterial hypertension of various degrees. Pulse wave velocity was measured in all patients. The correlation between pulse wave velocity vs age and systolic/diastolic blood pressure was calculated. The data obtained allowed to state that pulse wave velocity index has tight connection with blood pressure values. The authors reveal high statistical correlation between pulse wave velocity index and blood pressure values. The authors suppose that arterial stiffness might be the earlier diagnostic tool for to approaching vascular accident and, therefore, propose the pulse wave velocity index measurement in patients with initial signs of arterial hypertension.

Key words: vascular wall, vascular elasticity, stiffness, arterial hypertension, blood pressure, pulse wave velocity index

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ВИВЧЕННЯ ЖОРСТКОСТІ СУДИН У ХВОРИХ ЗАЛЕЖНО ВІД РІЗНИХ СТУПЕНІВ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ

Метою дослідження було визначення залежності жорсткості судин від значення артеріального тиску у хворих на артеріальну гіпертензію. Для клінічного спостереження були задіяні 90 осіб. Пацієнти були рандомізовані на 2 групи – 1 групу склали 15 здорових осіб. 2 групу склали 75 хворих на артеріальну гіпертензію різного ступеня. У всіх пацієнтів вимірювали швидкість пульсової хвилі. Розраховували кореляцію між швидкістю пульсової хвилі та віком і систолічним/діастолічним артеріальним тиском. Отримані дані дозволили стверджувати, що індекс швидкості пульсової хвилі, як характеристика еластичних властивостей судин, має тісний зв'язок із значеннями артеріального тиску. Автори виявили високу статистичну кореляцію між індексом швидкості пульсової хвилі та значеннями артеріального тиску. Автори припускають, що жорсткість артерій може бути раннім діагностичним критерієм судинної катастрофи,яка наближається, і тому пропонують вимірювати індекс швидкості пульсової хвилі у пацієнтів з початковими ознаками артеріальної гіпертензії.

Ключові слова: судинна стінка, еластичність судин, жорсткість, артеріальна гіпертензія, тиск крові, індекс швидкості пульсової хвилі

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Cardiovascular pathology remains one of the leading causes of death that's why the use of these disorders early markers remains highly relevant [8]. This is especially important concerning the arterial hypertension (AH) which prevalence throughout the world in older age patients acquires a "mass" character that requires the earliest diagnosis additionally to adequate therapy [13].

Vascular stiffness, being a characteristic of the vessel's elastic properties, is an independent predictor of general and cardiovascular mortality, fatal and non-fatal coronary events, severe strokes in patients with AH, type 2 diabetes, chronic renal failure with the increasing frequency in older persons [2, 5, 10].

Interestingly that vascular age definition comes to the forefront in the modern internal medicine [8]. Vascular aging refers to primary and/or secondary structural and functional changes affecting all layers of the arterial wall. The syndrome of early vascular aging (EVA) forms later which signs can be detected in the initial stages of the disease and sometimes in the subclinical stage [3, 7].

The pulse wave velocity (PWV) is considered to be the gold standard for arterial stiffness assessment [6]. PWV normal indexes were shown not be exceeded 10 m/s [1, 8]. Its moderate increase can be regarded as a sign of athero- and arteriosclerosis. The risk of cardiovascular complications increases by 11% with PWV 1 m/s increase [11].

The pathophysiological mechanisms of vascular stiffness in patients with AH are complex and not only involved the vascular media thickening and atherosclerosis formation [2]. The process of vascular remodeling is triggered simultaneously with the collagen synthesis intensification resulting in connective tissue matrix formation and vascular fibrosis develops. Its clear that vascular stiffness rats increases with the fibrosis formation.

Arterial stiffness might be decreased due to antihypertensive therapy, angiotensin-converting enzyme inhibitors, calcium blockers etc. [12]. The controversial data are present concerning the relationship between antihypertensive therapy and arterial stiffness that reveals the necessity of this question intensive study [9].

The purpose of the study was to investigate the dependence of vascular stiffness on blood pressure level in patients with arterial hypertension.

Materials and Methods. 90 people 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 (control group) was consisted of 15 conditionally healthy individuals. The group 2 was consisted of 75 patients with AH of various degrees.

The following criteria were used for the patient's inclusion into clinical observations: the patient's informed consent, AH of the 1st degree and AH of the 2nd degree. Exclusion criteria we used were the following: age over 59 years, cardiac rhythm and intracardiac conduction disturbances, 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. The mean age of healthy subjects (8 men and 7 women) was 23.40±1.96 years. Age of the patients with AH (44 men and 31 women) ranged from 27 to 59 years. The mean index was equal to 44.4±0.99 years.

To investigate the AH index influence on vascular stiffness the group 2 patients were divided also according the various degrees of AH on the following two subgroups: 39 patients with the 1st degree of AH (52.0 %) consisted the subgroup 1 and 36 patients with the 2nd degree of AH (48.0 %) consisted the subgroup 2. According to the study design the patients of “elderly” age according to WHO classification (60 years and older) were not included in the observation and in the group of patients with AH 1st degree belonged to the “young”, and in the group with AH 2nd degree – were referred to the “middle” age (38.2±1.04 years and 51.1±0.8 years, respectively). Patients with AH 1st and 2nd degree were comparable with each other by gender, age, and duration of disease.

In the other series of the clinical trial to study in details the correlation PWV vs blood pressure (BP) level we divided group 2 patients according to their systolic blood pressure (SBP) and diastolic blood pressure (DBP) values into the following 4 subgroups: subgroups with (a) SBP=140–149 mm Hg/ DBP=90–94 mm Hg, (b) SBP=150–159 mm Hg/ DBP=95–99 mm Hg, (c) SBP = 160–169 mmHg/ DBP=100–104 mm Hg and (d) SBP=170–179+ mmHg/ DBP=105–109+ mm Hg. PWV and correlations with a more detailed breakdown by SBP and DBP were studied in all subgroups.

PWV was measured using a specially designed original device using generally accepted carotid-femoral technique [14]. 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±m where M is the arithmetic mean and m is the standard error of the mean. 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 patients with AH 1st degree was equal to 9.8±0.2 m/s (with 6.7±0.4 in the control, p=0.0000) and almost reached its upper normative values (up to 10 m/s; Table 1).

Table 1

PWV in patients with AH and its correlation with systolic (SBP) and diastolic (DBP) blood pressure

Index	The examined patients		
	Group 1 (1)	Group 2 AH 1st degree, (2)	Group 2 AH 2nd degree, (3)
Mean age	23.4±0.5	38.2±1.0	51.1±0.8
PWV, m/s	6.7±0.4	9.8±0.2	10.9±0.2
Systolic BP, Hg.mm	118.5±1.3	148.4±0.9	167.7±1.1
Diastolic BP, Hg.mm	75.9±2.1	94.5±0.5	104±0.7
Spearman rank, r SBP-PWV	r=0.21	r=0.49	r=0.61
DBP-PWV	r=0.11	r=0.29	r=0.32

Note: PWV intergroup differences equal to p<0.001 – the significant differences 1vs 2 (t_{1-2}=7.29), 1 vs 3 (t_{1-3}=11.3) and 2 vs 3 (t_{2-3}=3.87) positions (Mann-Whitney U-test).

Even in patients younger 40 years with AH 1st degree PWV already increases, and the difference with the control value is significant (p=0.0000). The hypertension increases up to the 2nd degree resulted in significant PWV index increase reaching 10.9±0.2 m/s that already exceed the normal value (p=0.0000). It should me mentioned PWV index difference was already highly reliable in patients with AH 1st degree (p=0.0002 at t=3.87).

The next step of this analysis was to study correlation between PWV and systolic and diastolic blood pressure values in each of the group of the examined patients. It's evident that there is no "strong" correlation in both groups neither in systolic, nor in diastolic pressure, i.e. Spearman rank did not reach 0.7 or more. However, it should be noted that in both groups there was almost no correlation for blood pressure and the correlation was "weak" and "moderate" (Spearman's rank equal to 0.29 and 0.32, respectively), but for blood pressure in the group of patients with AH 2nd degree it reached the highest level (the "moderate") and equal to 0.61.

PWV indexes difference between healthy people (group 1) and the patients with SBP moderate increase (SPB=140-149 mm Hg) is highly significant (p<0.01; Table 2), even despite the fact that the stiffness index in the AH 1st degree subgroup has not exceeded its normal value (9.1±0.3 m/s). PWV indexes increased with BP increasing: PWV equal to 10.4±0.2 m/s at SBP=150–159, 10.6±0.2 m/s at SBP=160–169 and 11.5±0.2 m/s at SBP=170–179.)

Table 2

PWV in AH patients and the degree of its correlation with AH level

Index	The examined patients				
	Group 1 (1)	Group 2 AH 1st degree with SBP/DBP levels		Group 2 AH 2nd degree with SBP/DBP levels	
		140–149/ 90–94 mm Hg (2)	150–159/ 95–99 mm Hg (3)	160–169/ 100–104 mm Hg (4)	170–179+/ 105–109+ mm Hg (5)
Systolic BP, Hg.mm	118.5±1.3	143.2±0.7	153.4±0.6	163.7±0.8	174.7±0.9
Diastolic BP, Hg.mm	6.7±0.4	9.1±0.3	10.4±0.2	10.6±0.2	11.5±0.2
PWV, m/s	6.7±0.4	9.1±0.3	10.4±0.2	10.6±0.2	11.5±0.2
Spearman rank, r SBP-PWV	r=0.21	r=0.37	r=0.41	r=0.53	r=0.71
DBP-PWV	r=0.11	r=0.24	r=0.15	r=0.46	r=0.62

Note: PWV intergroup differences equal to p<0.001 – the significant differences 1vs 2 ($t_{1\text{-}2}$=4.9), 1 vs 3 ($t_{1\text{-}3}$=9.2), 1 vs 4 ($t_{1\text{-}4}$=9.3) and 1 vs 5 ($t_{1\text{-}5}$=10.9) positions (Mann-Whitney U-test).

These data confirm the above conclusion after preliminary data analysis concerning the direct dependence of arterial wall stiffness with arterial blood values increasing. Our data for more visual clarity are present on Fig. 1.

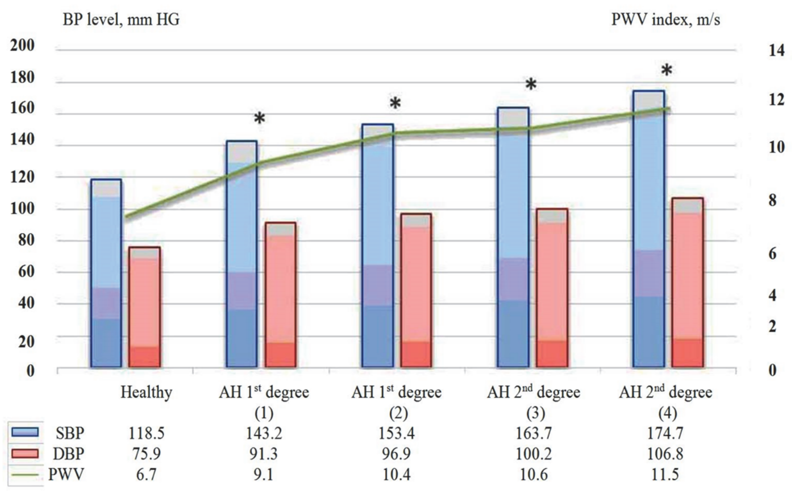

Fig. 1. The influence of arterial blood pressure values on PWV index. * – p<0.05 – the significant PWV indexes increase vs the same in group 1 (Mann-Whitney U-test).

The data obtained were confirmed by a more detailed correlations calculation between PWV and "ranked" blood pressure subgroups. Thus, in subgroup 1 (SBP=140–149 mm Hg) there was a "mean" (r=0.37) correlation PWV vs SBP. In the second (SBP=150–159 mm Hg) and the third (SBP=160–169 mm Hg) subgroups the correlation strength continued to be increase (r=0.41 and r=0.53, respectively) reaching maximal index in patients of the 4th subgroup with the highest SBP=170–179+ mmHg (r=0.71, "high" correlation).

Similar results we received while studying the correlation PWV vs DBP values. Thus, in subgroups 1 and 2 (DBP=90–94 mm Hg and (DBP=95–99 mm Hg) this relationship was assessed as "low" (r=0.24 and r=0.15, respectively). As DBP increased till to 100-104 mm Hg (the 3rd subgroup) the strength of association was already estimated as "medium" (r=0.46), reaching its maximal value DBP of 105–109+ mm Hg ("medium" but with higher Spearman rank, r=0.62). Correlation PWV vs SBP, being sometime similar with DBP data, were more expressed at earlier stages of arterial hypertension.

Therefore, the data obtained and their analysis allowed to state that PWV index, being the characteristic of vessels' elastic properties, has tight connection with blood pressure values. We performed a detailed analysis of PWV index changes depending on both blood systolic and diastolic pressure "step-by-step" change together with statistically calculated correlations between the PWV changes dependence vs the blood pressure indexes gradients. These data coincide with the results of clinical observations in which vascular stiffness, from one side, is considered to be an age-related process that results from adverse changes in the structure and function of the elastic arterial vessel wall [4, 15] and, from the other side, is corresponded with vascular damage in patients with metabolic syndrome and obesity which is well-known by vascular pathology predominant pathophysiological mechanisms [2].

We proved high statistical correlation between PWV index and BP values and hence we could suppose that arterial stiffness is the valid predicting index for AH development. The interesting diagnostic, prognostic and even philosophical question if the following: can we consider the AH as the pathological event in the organism that determine or even accelerate the arterial stiffness formation? Our data analysis and published scientific results allow to answer positively as, for instance, diabetes with known vascular pathology could accelerate the process of arterial stiffness [10].

In 2019, leading experts in the field of vascular stiffness research confirmed the position that arterial stiffness is the best index of the combined effect of known and unknown risk factors of arterial wall damage and proposed to express very high and very low arterial stiffness in terms of EVA and SUPERNOVA (supernormal vascular aging). With the SUPERNOVA phenotype, patients have extremely low vascular stiffness values for their age and gender. There is a suggestion that, for some yet unexplored reason, exposure to cardiovascular risk factors does not lead to subclinical organ damage and cardiovascular complications [6]. The answer, we believe, is hidden in the pathophysiological mechanisms of the disease.

The important and interesting are the pathophysiological vascular changes mechanisms occurring with AH and thus determining the vascular stiffness formation. From this point of view one should remember that characteristic features occurring in large and small arteries during AH development and during aging include endothelial dysfunction, vascular remodeling, inflammation, calcification and, as the result of these chain pathophysiological events, increased stiffness. One could see an endothelial cell damage, increased vascular smooth muscle cell growth, inflammatory cell migration, extracellular matrix deposition, fibrosis and calcification at the cellular level [3]. And what is prognostically dangerous – there is a report that young patients with high BP level already have arterial changes, similar to those in older people with normal BP w. h, firstly, suggests "premature" vascular ageing, secondly, shows evidences of vessels walls involvement into pathological events in hypertension, and, thirdly, proves that hypertension does accelerate age-related vascular changes [5].

With this regard, we believed extremely interesting to investigate the PWV index in AH patients of younger age as well as their vascular stiffness together with its possible correlation vs SBP and DBP. We didn't find any related works on this topic in the analyzed literature.

Briefly, all our patients of with AH 1st degree were "young" (38.2±1.04), and according to results of population studies regarding to age ranking their PWV should be in the range between 5.2–8.0 m/s and normally should not exceed 8.0 m/s [1]. Our results become even more convincing taking into account that patients with AH 2nd degree belonged to "mean" age group (51.1±0.8) which normal PWV index should be in the range of 6.3–10.0 m/s [1].

The data obtained allow to conclude that both not elderly patients (less than 60 years) and "young" (according to WHO) aged patients with AH 1st degree have significantly increased vascular stiffness further increasing with age ("mean" by WHO definition) and AH level (AH 2nd).

A certain increase in the PWV/AH degree ratio is explained, we suppose, by the SBP higher values in the 2nd subgroup (167.7±1.1 mm Hg vs 148.4±0.9 mm Hg in AH 1st degree). However, it should be stressed that this group includes older patients (51.1±0.8 years vs 38.2±1.04 years for AH 1st degree), which means that the probability of other mechanisms joining that increase the vascular wall stiffness.

We have to remember the comorbid pathology in patients with AH aged after 50 years that can "contribute" to the vascular walls elastic properties change.

The findings indicated the evidenced effect of arterial stiffness on the blood pressure increase and therefore arterial hypertension development. We suppose that arterial stiffness might be the earlier diagnostic tool for to approaching vascular accident. Therefore, we propose the PWV index measurement in patients with initial signs of arterial hypertension.

Conclusions

1. PWV index, being the characteristic of vessels' elastic properties, has tight connection with blood pressure values.

2. Arterial stiffness is the valid predicting index for AH development

3. The level of vascular stiffness increases with the degree of arterial hypertension, not only in elderly patients, but also in "young" and "middle-aged" patients according to the WHO classification.

4. There is a "medium" to "strong" correlation (Spearman's coefficient = 0.53–0.71) between PWV and systolic blood pressure as the latter increased. The correlation between a PWV and diastolic blood pressure is significantly weaker and is at the level of "weak" and "mean" (0.46–0.62).

5. PWV index determination to assess vascular elastic properties is an informative and easy-to-use method recommended for use in patients with cardiovascular pathology, particularly with arterial hypertension.

Prospects for further research include a subsequent comprehensive clinical observation of groups of patients with arterial hypertension at different ages to evaluate the strict dependence between PWV index and blood pressure values. PWV index and arterial stiffness should be regarded and the diagnostic earlier subclinical features of the vascular pathology that approaches.

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