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FEATURES OF THE CLINICAL COURSE OF NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME DEPENDING ON THE INDICATOR OF THE PULSE WAVE VELOCITY

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Abstract. Pulse wave velocity (PWV) could be used as a predictor of the course of CVD. A carotid–femoral PWV above 10 m/s was determined in 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension as factors influencing cardiovascular risk in patients with hypertension. Exactly the carotid–femoral PWV is considered the gold standard for arterial stiffness assessment in clinical practice. Usually PWV predict the long-term outcomes (in a few month or years) of the development of cardiovascular events. There are a lack of information about using PWV as prognostic marker in acute coronary syndrome.

The aim: to study the features of the clinical course of the non-ST-segment elevation acute coronary syndrome (NSTE-ACS) depending on the carotid–femoral pulse wave velocity (PWV) and find out possibilities of using PWV as marker of intrahospital clinical outcomes.

Materials and methods. 80 patients were recruited. All patients were hospitalized into myocardial infarction departments with a diagnosis of NSTE-ACS. Patients over 18 years of age who were hospitalized for the first 3 days after the onset of pain and signed the agreement to participate in the study were included. Exclusion criteria were the moderate or severe anemia, severe chronic renal failure, and chronic diseases in the acute or decompensated stage. The average age of patients was 64.5 [55; 72] years. Male patients are 45 persons (56.3%). Were performed standard general laboratory and instrumental examinations. Measuring of free DNA levels, and ischemic albumin were performed on 1st and 6th days of hospitalization. Also noninvasive measured of PWV. Noninvasive PWV measurements were performed after stabilization of the hemodynamic for excluding incorrect results due to its strong connection with current blood pressure. 2 groups were formed depend on the PWV above or less than 10 m/s. The analysis was performed by using non-parametric statistical methods (Mann-Whitney test, Wilcoxon T-test, Pearson's $\chi 2$ test). The results were considered statistically significant at $p < 0.05$.

Results. Patients did not have a statistically significant difference in such parameters as gender, anamnestic data (hypertension, myocardial infarction, chronic heart failure, atrial fibrillation, and diabetes mellitus), hemodynamic parameters, ECG changes at the moment of hospitalization and laboratory parameters. There was a tendency that patients with elevated PWV were older (69 [55.3; 77.8] years vs. 63.5 [55.3; 70.8] years) ($p = 0.077$). Such parameters as left ventricular ejection fraction and discharge diagnosis were similar. Patients with elevated PWV had significantly more active cytolysis. This is proved by significantly higher levels of free DNA both on the first day and on the 6th day of hospitalization. In patients with normal PWV levels, free DNA decreased in dynamics, while in patients with PWV above 10 m / s this marker remained at the same level. It was also founded that patients with elevated PWV had delayed ischemia (on the 6th day of hospital stay), which was confirmed by a higher level of ischemia-modified albumin than in the group with PWV less 10 m / s.

Conclusions. Patients with increased and normal PWV have quite similar group characteristic according typical clinical signs, results of laboratory and instrumental investigations. Due to the studying of free DNA and ischemia-modified albumin were clarified that PWV above 10 m/s is associated with delayed ischemia and longer tissue damage and could be used to predict it.

Keywords: acute coronary syndrome, pulse wave velocity, prognosis, hospital stage.

Introduction. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally [1]. Arterial stiffness (AS) is a predictor of coronary artery outcomes in patients with CVD [2]. From clinical point of view, recognition, and measurement of arterial stiffness is important, because increased arterial stiffness is associated with worse cardiovascular outcomes, independent of traditional risk factors such as aging, hypertension, diabetes, dyslipidemia, obesity, and smoking [3]. Carotid–femoral pulse wave velocity is a commonly used method for assessing AS [2]. Increased aortic stiffness, assessed by PWV, contributes significantly to cardiovascular death [4].

PWV correlation and different CVD is studied in numerous researches. PWV is well-correlated with the presence and extent of coronary, cerebral, and carotid atherosclerosis [3]. There was found a positive linear correlation between carotid intima-media thickness and PWV in general population [5] and in case of hypertensive [1]. İsmail S. et al. showed that PWV is an Independent Predictor of Office Hypertension [6].

In high cardiovascular risk patients, an age-dependent association of PWV with coronary artery disease and diastolic dysfunction was evinced [7]. PWV could be used as universal tool for risk assessment for patients with stable forms of CVD, for patients with

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unstable ones, same as for persons without manifestated CVD. PWV may offer insight into CVD and all-cause mortality risk beyond traditional CVD risk factors in the general population [8].

Justification of the research. According to the two targeting arteries, various types of PWV measurements were determined such as carotid-femoral PWV and brachial-ankle pulse wave velocity [3]. Exactly the carotid–femoral PWV is considered the gold standard for arterial stiffness assessment in clinical practice [9].

There are some research works which try to find out the prognostic value of PWV for acute coronary syndromes (ACS). Das PR et al. found out that PWV in NSTEMI can detect high risk patients requiring an early invasive strategy over a delayed invasive strategy [10]. Measurements of aortic PWV in NSTEMI can detect high risk patients requiring an early invasive strategy over a delayed invasive strategy [10].

PWV measurement increases the prognostic power for cardiac events in patients with acute myocardial infarction [11].

AS estimation in patients with diabetes mellitus 2 type after STEMI discriminate patients at higher risk for 3-year recurrence, and maybe valuable for distinguishing patients likely to require a more rigorous therapeutic intervention [12]. In the multivariate analysis PWV showed the ability to predict the outcome in terms of EF recovery at 3 and 6 months also after any correction for age and other variables ($\beta = -0.566$, $p < 0.001$). Increased arterial stiffening may result in a less effective recovery of LV function after acute myocardial infarction [13].

Therefore, on the one hand there are numerous researches about connection between PWV and CVD, and on the other hand there is a lack of works about PWV and ACS, especcialy Non-ST-segment-elevation ACS.

The another problem is, that researchers mainly pay attention for long term outcomes or miocardial infarction risk on the background of another diseases and conditions and miss to study intrahospital outcomes.

The feature of provided research is to figure out pecularities of clinical course in patients with acute coronary syndrome without ST elevation depends on PWV level.

The aim: to study the features of the clinical course of the non-ST-segment elevation acute coronary syndrome (NSTE-ACS) depending on the carotid–femoral pulse wave velocity (PWV) and find out possibilities of using PWV as marker of intrahospital clinical outcomes.

Materials and methods. The study group included 80 patients diagnosed with NSTE-ACS who were hospitalized in the first 72 hours after the onset of anginal attack and signed consent for participation in the research. Patients with moderate and severe anemia, severe chronic renal failure and chronic exacerbations or decompensated chronic diseases were excluded. The diagnosis of NSTE-ACS was based on the presence of typical anginal pain and the ECG patterns.

Clinical (collection of complaints and anamnesis, objective examination), laboratory (general clinical blood test, renal and hepatic complex, lipid profile, glucose, troponin T and instrumental examinations (ECG, echocardiography with emission fraction (EF)) were performed. Glomerular filtration rate (GFR) was calculated using the MDRD formula.

In addition to the standard clinical and biochemical examination on admission to the hospital, the level of troponin T (ELISA method; normal level <0.014 ng / ml), ischemic albumin (IMA), cobalt-binding albumin spectroscopy (ELISA), free DNA (ELISA). PWV (m / s) was measured using the apparatus of VAT 41-2 (Kyiv, Ukraine).

Patients were divided into 2 groups, depending on PWV: with PWV less than 10 m / s (PWV <10 m / s) and PWV above 10 m / s (PWV> 10 m / s). The group of patients with normal PWV included 58 patients, and the PWV> 10 m / s group - 22. A more detailed description of the groups will be given in the results of the study. All patients received treatment according to the Ukrainian and European guidelines for the treatment of NSTE-ACS.

Statistical analysis. Statistical analysis was performed by using MS Excel, Statistica 6.0 (serial number AGAR 909E415822FA). Due to calculating the Shapiro-Wilk test, a nonparametric distribution was found for most parameters, so nonparametric criteria were used to present and calculate the significance of differences between groups. The median was used to describe the quantitative parameters of the groups, indicating the interquarter range (25 and 75 percentiles) (Me [Q1; Q3]). The prevalence of the phenomenon in the groups was described in percentage and absolute number of patients and was indicated in tables n (%). Nonparametric criteria were used for the calculations (Mann-Whitney test, Wilcoxon T-test, Pearson's $\chi 2$ test, including for arbitrary tables). The results were considered statistically significant at $p < 0.05$ [A].

Results. The number of men and women was similar in both groups (Table 1). Women with normal PWV levels tend to have higher PWV.

Table 1

Gender and average PWV levels

Groups	Male	Male patients	p* (male vs female)	Female	Female patients
PWV >10 m/s	10.7 [10.45; 10.9]	11 (50%)	0.39	10.5 [10.3; 11]	11 (50%)
PWV <10 m/s	8.2 [7.9; 8.8]	34 (57.8%)	0.057	8.65 [8.175; 9.375]	24 (42.2%)

Note: * the Mann-Whitney test to assess the reliability of the difference in quantitative indicators between groups.

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Table 2

PWV indicators in groups depending on age

Age groups	PWV >10 m/s		PWV <10 m/s	
	Patient quantity	Me [Q1;Q3]	Patient quantity	Me [Q1;Q3]
40-49	1 (4.6%)	NA	7 (11.9%)	8,7 [8,2;8.8]
50-59	6 (27.3%)	10.8 [10.6;10.9]	13 (22.1%)	8,4 [8;9.3]
60-69	5 (22.6%)	10.4 [10.4; 10.5]	21 (37.1%)	8,2 [7,8;9.2]
70-79	6 (27.3%)	10.9 [10.3;11]	12 (20.4%)	8,6 [8,2;9.2]
≥80	4 (18.2%)	10,9 [10.2;11.7]	5 (8.5%)	8,8 [8,6;9.6]

The mean age in the group with PWV>10 m/s was higher than in normal PWV (69 [55.3; 77.8] versus 63.5 [55.3; 70.8]) (p = 0.077). Table 2 shows the age composition of the groups. A statistically significant difference was found only between the age subgroups 50-59 years and 60-69 years among patients with PWV>10 m/s (p = 0.04). The detected increase in PWV in young patients (50-59 years) is associated with the presence in the group of statistical emissions (1 patient had a very high level of PWV - 11.8 m / s), which led to distortion of the results.

Table 3 shows that arterial hypertension (AH), previous myocardial infarction (MI), chronic heart failure (CHF), atrial fibrillation (AF) and diabetes according to $\chi 2$ criteria are not associated with PWV levels.

Hemodynamic parameters (Table 4) were similar in the group with elevated and normal PWV.

Pearson's $\chi 2$ criteria (0.028; p = 0.868) was calculated to compare patient groups by PWV level and probability of developing acute left ventricular failure. It does not show association between these parameters (Table 5).

Table 3

Anamnestic characteristics of groups

Parameter	PWV >10 m/s	χ^2	p	PWV <10 m/s
AH	18 (81.9%)	0.063	0.803	46 (78.2%)
Previous MI	6 (27.3%)	0.084	0.773	14 (23,.%)
CHF	11 (50%)	0.307	0.58	25 (42.5%)
AF	5 (22.8%)	0.018	0.895	14 (23.8%)
Diabetes melitus	3 (13.7%)	0.044	0.834	9 (15.3%)

Table 4

Hemodynamic parameters at the moment of hospitalization depending on PWV

Hemodynamic parameters	PWV >10 m/s	p (PWV >10 m/s vs PWV <10 m/s)	PWV <10 m/s
SBP, mm Hg	145 [132.5;157.5]	0.098	140 [120;150]
DBP, mm Hg	80 [80;90]	0.25	85 [80;90]
Pulse, beats/min	79.5 [70.5;83.5]	0.47	78 [70;86]

Table 5

Number of patients with acute left ventricular failure (according to Killip) at the time of hospitalization depending on PWV

Parameter	PWV >10 m/s	PWV <10 m/s
Killip I	20 (91%)	52 (89.8%)
Killip II	2 (9%)	5 (8.5%)
Killip III	0	1 (1.7%)

Table 6

ECG changes during hospitalization depending on PWV

Parameter	PWV >10 m/s	p (PWV >10 m/s vs PWV <10 m/s)	PWV <10 m/s
ST depression	17 (77.4%)	0.156	38 (64.6%)
T inversion	9 (41%)	0.39	30 (51%)

There were no typical ECG changes for groups with normal and elevated PWV (Table 6). The severity of ST depression was similar in both groups: 4 [2; 8] mm in group with normal PWV and 4 [2.25; 6] mm in group PWV>10 m / s (p = 0.45).

To confirm the significance of differences between groups (Table 7), Pearson's $\chi 2$ criteria was calculated for arbitrary tables, which was 0.394 (p = 0.268). This indicates a lack of association between PWV and final diagnoses.

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Table 7

Final diagnoses in groups depending on PWV

Groups	Q myocardial infarction	nonQ myocardial infarction	Unstable angina
PWV >10 m/s	2 (9.1%)	15 (68.1%)	5 (22.8%)
PWV <10 m/s	2 (3.4%)	42 (72.8%)	14 (23.8%)

Table 8

Left ventricular ejection fraction (EF) values depending on PWV

Groups	EF <40%	EF 40-49%	EF ≥50%
PWV >10 m/s	2 (9.1%)	2 (9.1%)	18 (81.8%)
PWV <10 m/s *	4 (6.8%)	10 (17%)	41 (76.2%)

Note: * - 3 patients did not done echocardiography.

To confirm the significance of differences between groups (Table 8), Pearson's $\chi 2$ criteria was calculated for arbitrary tables. It was 1.149 (p = 0.563). This indicates the insignificance of the difference between groups and the insignificance of PWV on EF.

Table 9

Biochemical parameters depending on PWV

Laboratory tests	PWV >10 m/s	p (PWV >10 m/s vs PWV <10 m/s)	PWV <10 m/s
Troponin T	0.03 [0.012;0.084]	0.43	0.038 [0.009;0.092]
Creatinin	96 [85.1;105.7]	0.34	97.1 [88.8;108.3]
GFR	66.9 [52.6;74.3]	0.23	60.9 [48.2;71.7]
Total cholesterol	4.6 [3.8;5.7]	0.46	4.7 [3.8;5.74]
LPHD	2.51 [1.75;3.26]	0.3	2.66 [1.92;3.38]
Triglycerides	1.28 [1.045;1.715]	0.48	1.33 [1.113;1.483]
D-dimer	515.9 [262;897.75]	0.1	393.5 [333.75;583.25]

There was a tendency that patients with elevated PWV had higher levels of D-dimer (p = 0.1) (table 9). Among patients with elevated D-dimer, patients with PWV> 10 m / s had a higher D-dimer 619.5 [448.25; 1362] vs 437 [360.75; 633.75] than patients with PWV <10 m / s (p = 0.044). All other biomarkers did not show significant difference between groups.

Table 10 shows that patients with PWV> 10 m / s had a longterm ischemia, according to the level of IMA, during the hospital period. Patients with elevated PWV levels had statistically higher IMA levels on 6th day of hospitalization (p = 0.04).

Table 10

Indicators of ischemia-modified albumin (IMA) on the 1st and 6th day of hospitalization depending on the level of PWV

	PWV >10 m/s	p (PWV >10 m/s vs PWV <10 m/s)	PWV <10 m/s
IMA 1st day	0.458 [0.407;0.503]	0.34	0.451 [0.387;0.498]
IMA 6th day	0.434 [0.414;0.499]	0.04	0.403 [0.349;0.469]

Table 11

Free DNA levels on the 1st and 6th day of hospitalization depending on the PWV level

	PWV >10 m/s	p (PWV >10 m/s vs PWV <10 m/s)	PWV <10 m/s
DNA 1st day	488 [312.5;698]	0.022	314 [237.3;448.5]
DNA 6th day	481 [419.8;693]	0.039	282 [230;367]

Analysis of the level of free DNA in the blood plasma showed that patients with elevated PWV had a higher level of cytolysis both at the time of hospitalization (p = 0.022) and in the late hospital period (p = 0.039).

Discussion. The analyzed results demonstrate the insignificance of the relationship between PWV and the analyzed factors, parameters (gender, age, anamnestic data, hemodynamic parameters and ECG changes). This may indicate the possibility of using PWV as an independent marker for predicting the course of NSTE-ACS in the hospital stage.

It was found that PWV> 10 m / s is can be used for the prognosis of prolonged and delayed ischemia in patients with NSTE-ACS. None of the patients, regardless of PWV level, complained to anginal pain at the discharge. This suggests the possibility of using PWV as a marker of silent long-term and delayed ischemia in patients with NSTE-ACS.

Also, patients with elevated PWV have more pronounced cytolysis, as evidenced by the level of free DNA. Moreover, in this group there were statistically higher levels of free DNA, both at the 1st and on the 6th day. Free DNA decreased in dynamics in patients with

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normal PWV. While the DNA level in patients with PWV above 10 m / s remained at the same level.

Conclusions. Patients with elevated and normal PWV have quite similar characteristics according to typical clinical signs, results of laboratory and instrumental studies. Studies of free DNA and ischemia-modified albumin have shown that PWV above 10 m / s is associated with delayed silent ischemia and longer-term tissue damage and can be used to predict it.

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ОСОБЛИВОСТІ КЛІНІЧНОГО ПЕРЕБІГУ ГОСТРОГО КОРОНАРНОГО СИНДРОМУ БЕЗ ЕЛЕВАЦІЇ СЕГМЕНТУ ST У ЗАЛЕЖНОСТІ ВІД ПОКАЗНИКІВ ШВИДКОСТІ ПУЛЬСОВОЇ ХВИЛІ

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Резюме. Мета. Дослідити особливості клінічного перебігу гострого коронарного синдрому без підйому сегмента ST (ГКСбеST) залежно від швидкості каротидно-стегнової пульсової хвилі (PWV) та з'ясувати можливості використання PWV як маркера внутрішньолікарняних клінічних виходів.

Матеріали та методи. Обрано 80 хворих, що були госпіталізовані в інфарктні відділення з діагнозом ГКСбеST. Включались пацієнти, старші за 18 років, госпіталізовані у перші 3 доби від початку больового синдрому та які дали згоду на участь у дослідженні. Виключались хворі з анемією середнього та тяжкого ступеня, хронічною нирковою недостатністю важкого ступеню та хронічними захворюваннями у стадії загострення або декомпенсації. Окрім стандартних загальноклінічних лабораторних та інструментальних досліджень, пацієнтам вимірювались PWV, рівні вільної ДНК, ішемізованого альбуміну на 1 та 6 день госпіталізації.

Результати. Пацієнти не мали статистично достовірної різниці за такими параметрами як стать, анамнестичні дані, гемодинамічні показники, ЕКГ-зміни та лабораторні показники. За такими параметрами як фракція викиду лівого шлуночка та заключний діагноз групи були подібними. Пацієнти з підвищеною

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PWV мали достовірно більш активний цитоліз, що підтверджено більш високими рівнями вільної ДНК як у перший день, так і на шостий день госпіталізації. У пацієнтів з нормальним рівнем PWV вільна ДНК у динаміці знизилась, у той час як у пацієнтів з PWV >10 м/с цей маркер залишився на тому ж рівні. Пацієнти з підвищеною PWV мали відстрочену ішемію (на 6-ий день перебування у стаціонарі), що було підтверджено рівнем ішемізованого альбуміну.

Висновки. Не виявлено достовірного зв'язку PWV зі стандартними клінічними даними, але PWV може використовуватись для прогнозування відстроченої ішемії та асоціюється з тривалим ураження тканин.

Ключові слова: гострий коронарний синдром, швидкість пульсової хвилі, прогноз, госпітальний етап.

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