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

O.S. Shchukina

Dnipro State Medical University, Department of Internal Medicine 3, Dnipro, Ukraine, ORCID ID: 0000-0002-9543-1545, e-mail: shchukina.olina@gmail.com

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 χ2 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; 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 parameters, ECG changes at the moment of hospitalization and laboratory parameters. There was a tendency that patients with elevated PWV had significantly more acute 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].
Unstable ones, same as for persons without manifested 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 (β = -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, especially Non-ST-segment-elevation ACS.

The another problem is, that researchers mainly pay attention for long term outcomes or myocardial 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 peculiarities 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 interquartile 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 χ2 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.

| Groups     | Male | Male patients | p* (male vs female) | Female | Female patients |
|------------|------|---------------|---------------------|--------|-----------------|
| PWV >10 m/s| 10.7 | 11 (50%)      | 0.39                | 10.5   | 11 (50%)        |
| PWV <10 m/s| 8.2  | 34 (57.8%)    | 0.057               | 8.65   | 24 (42.2%)      |

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

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 χ² criteria are not associated with PWV levels.

Table 4 shows that hemodynamic parameters (Table 4) were similar in the group with elevated and normal PWV. Pearson's χ² 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 5 shows that 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).
ACS in the hospital stage. This may indicate the possibility of using PWV as an independent marker for predicting the course of NSTE-ACS in the hospital stage.

Table 7

| Final diagnoses in groups depending on PWV |
|--------------------------------------------|
| Groups                                | Q myocardial infarction | non-Q 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 χ² criteria was calculated for arbitrary tables. It was 1.149 (p = 0.563).

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

| Indicators of ischemia-modified albumin (IMA) on the 1st and 6th day of hospitalization depending on the level of PWV |
|----------------------------------------------------------------------------------------------------------------|
| IMA 1st day | p (IMA 1st day vs IMA 6th day) | IMA 6th day | p (IMA 1st day vs IMA 6th day) |
| PWV >10 m/s | 0.458 [0.407;0.503] | 0.34 | 0.451 [0.387;0.498] |
| PWV <10 m/s | 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 |
|-----------------------------------------------------------------------------------|
| DNA 1st day | p (DNA 1st day vs DNA 6th day) | DNA 6th day | p (DNA 1st day vs DNA 6th day) |
| PWV >10 m/s | 0.022 | 314 [237.3;448.5] |
| PWV <10 m/s | 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...
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.

References:
1. Benjamin E, Virani S, Callaway C, Chamberlain A, Chang A, Cheng S, et al. Heart Disease and Stroke Statistics — 2018 Update: A Report From The American Heart Association. Circulation. 2018; 137(12):e67-e492. DOI: 10.10880/10641963.2018.1506471
2. Zhong Q, Hu M, Cui Y, Liang L, Zhou M, Yang Y, et al. Carotid–Femoral Pulse Wave Velocity in the Prediction of Cardiovascular Events and Mortality: An Updated Systematic Review and Meta-Analysis. Angiology. 2017; 69(7):617-629. DOI: 10.1177/0003319717742544
3. Kim H, Kim S. Pulse Wave Velocity in Atherosclerosis. Frontiers in Cardiovascular Medicine. 2019; 6:41. DOI: 10.3389/fcmvm.2019.00041
4. Regnault V, Lagrange J, Pizard A, Safar M, Fay R, Pitt B, et al. Opposite Predictive Value of Pulse Pressure and Aortic Pulse Wave Velocity on Heart Failure With Reduced Left Ventricular Ejection Fraction. Hypertension. 2014; 63(1):105-111. DOI: 10.1161/HYPERTENSIONAHA.113.02046
5. Lu Y, Zhu M, Bai B, Chi C, Yu S, Teliewubai J, et al. Comparison of Carotid-Femoral and Brachial-Ankle Pulse-Wave Velocity in Association With Target Organ Damage in the Community-Dwelling Elderly Chinese: The Northern Shanghai Study. Journal of the American Heart Association. 2017; 6(2):e004168. DOI: 10.1161/JAHA.116.004168
6. Ismail S, Ömer Ş, Hakan D, Ali Gokhan O, Murtaza Emre D. Pulse Wave Velocity is an Independent Predictor of Office Hypertension. International Journal of Clinical Cardiology. 2021; (8):4(233). DOI: 10.23937/2378-2951/14.102324
7. Georgiopoulou G, Papaioannou T, Magkas N, Laina A, Mareti A, Georgiou S, et al. Age-dependent association of pulse wave velocity with coronary artery disease and myocardial aging in high-risk patients. Journal of Cardiovascular Medicine. 2019; 20(4):201-209. DOI: 10.2459/JCM.0000000000000769
8. Hefferman K, Jae S, Loprinzi P. Association Between Estimated Pulse Wave Velocity and Mortality in U.S. Adults. Journal of the American College of Cardiology. 2020; 75(15):1862-1864. DOI: 10.1016/j.jacc.2020.02.035
9. Milan A, Zocaro G, Leone D, Tosello F, Buraiali I, Schiavone D, et al. Current assessment of pulse wave velocity. Journal of Hypertension. 2019; 37(8):1547-1557. DOI: 10.1097/HJH.0000000000002081
10. Das P, Razzaque M, Ahmed R, Islam S, Barman R, Khan A, et al. Association of Aortic Pulse Wave Velocity with the Severity of Coronary Artery Disease in Patients with Non-ST-Segment Elevation Myocardial Infarction. Bangladesh Heart Journal. 2021; 36(1):38-46. DOI: 10.3329/bjh.v36i1.55516
11. Park H, Kim H, Kang M, Kim K, Koh J, Park J, et al. Predictive value of the combination of brachial-ankle pulse wave velocity and ankle-brachial index for cardiovascular outcomes in patients with acute myocardial infarction. Coronary Artery Disease. 2020; 31(2):157-165. DOI: 10.1097/MCA.0000000000000777
12. Levisianou D, Foussas S, Skopelitis E, Adamopoulos E, Xenopoulou T, Destounis O, et al. Arterial stiffness predicts risk for long-term recurrence in patients with type 2 diabetes admitted for acute coronary event. Diabetes Research and Clinical Practice. 2013; 99(3):315-320. DOI: 10.1016/j.diabres.2012.11.023
13. Imbalzano E, Vatrano M, Mandraffino G, Ghiaodoni L, Gangemi S, Bruno R, et al. Arterial stiffness as a predictor of recovery of left ventricular systolic function after acute myocardial infarction treated with primary percutaneous coronary intervention. The International Journal of Cardiovascular Imaging. 2015; 31(8):1545-1551. DOI: 10.1007/s10554-015-0733-8
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 відсрочену 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.

Стаття надійшла в редакцію 21.02.2022 р.
Стаття прийнята до друку 16.03.2022 р.