PROSPECTS FOR NT-pro BNP LEVEL DETERMINING IN PHYSICAL ACTIVITY CONDITIONS IN PATIENTS DURING THE REHABILITATION PERIOD AFTER THE MYOCARDIAL INFARCTION, COMPlicated WITH DECOMPENSATED HEART FAILURE

Ihor Vakaliuk
Department of Internal Medicine No 2 and Nursing

Khrystyna Levandovska
Department of Internal Medicine No 2 and Nursing
levandovska87@ukr.net

Natalia Tymochko
Department of Internal Medicine No 2 and Nursing

1Ivano-Frankivsk National Medical University
Halytska str., 2, Ivano-Frankivsk, Ukraine, 76018

Abstract
The aim of the study was to determine the futility of NT-pro BNP level analysis during dosed physical exercise for diagnosing decompensated HF in the postinfarction period and the possibility to determine the HF functional class.

Materials and methods. 160 patients with previous MI were examined, patients’ average age was (56.67 ± 5.72) years. The patients were randomized in 2 groups dependently on the presence of the signs of II A-B according to V. Kh. Vasylenko and M. D. Strazhesko classification and FC III-IV (according to NYHA) decompensated chronic HF. Group I consisted of 120 patients with Q-QS and non-Q MI; group II (the control one) had 40 patients with MI without signs of decompensated HF; 20 healthy people made up a norm group.

Results. Signs of coronary insufficiency such as dizziness and signs of poor peripheral perfusion (cyanosis/paleness) occurred in 104 (86.7 %) and 79 (65.8 %) cases that differ from the same values in the second group 4 (10.0 %) and 14 (35.0 %) respectively. 88 (73.3 %) patients with the signs of decompensated HF felt general weakness, fatigue, and expressed a request to stop the test.

The HR in the postinfarction patients with the signs of decompensated HF was before the exercise (88.2 ± 3.18) bpm (p ≤ 0.05); in the patients with past MI without the signs of decompensated HF, it was (75.32 ± 3.41) bpm (p ≤ 0.05); and in the practically healthy people, it was (77.73 ± 3.02) bpm. We found out a reverse moderate correlation between the distances that had been covered by a patient during the 6MWT NT-proBNP level in blood serum of examined patients.

Conclusions. Inadequate response to dosed physical exercises and increased immunological parameters as quantitative HF markers could be useful not only for diagnostics, but also for the risk stratification for decompensated HF that had occurred in patients on different rehabilitation stages after an acute MI.

Keywords: postinfarction period, six minutes walk test, decompensated heart failure, NT-proBNP.

DOI: 10.21303/2504-5679.2021.001793

1. Introduction
It is known that cardiovascular diseases (CVD) are the cause of about a third of lethal cases in the whole world, causing also a large number of disabilities that lead to significant economic losses in general [1]. Chronic heart failure (CHF) stays in the position of a state that is a potentially dangerous stage of any cardiovascular disease while demonstrating steady wide-spreading in the general population that is accompanied by economic expense progressive increase in the healthcare system regarding improving patients’ clinical status, their life quality, a decrease of death risk [2]. So, despite significant dynamics in the improved survival rate of patients with ischemic heart disease (IHD), MI is still one of the main causes of mortality in the world [3]. HF is a very frequent, “epidemic” disease of the whole world, which lies heavy on and pressures constantly the healthcare system with significant mortality, morbidity, and necessity of frequent rehospitalizations [4]. The fact deserves attention that the clinical evaluation of CHD severity is based on functional class (FC)
verification according to the NYHA classification, often not associated to left ventricular ejection fraction (LVEF) and prognostic biomarker levels, like N-terminal prohormone of brain natriuretic peptide, galectin-3, sST2, cardiac-specific troponin [5]. Large epidemiologic studies (ADHERE, OPTIMIZE-HF, EHFS I, II, ESC-HF, ALARM-HF) showed that hospital mortality of patients admitted with the diagnosis acute decompensated HF ranges from 4 % to 7 % excluding the ALARM-HF study, in which mortality was 11 %. The mortality during the first 3 months after the hospital discharge was from 7 % to 11 %, the mortality in the patients hospitalized due to acute decompensated HF during the first year after the hospital discharge reached 30 %, and 36 % in the ADHERE register that gives a right to consider HF one of leading problems in medicine [6, 7].

Significant general weakness is one of the main signs of HF and its further course, but its subjective evaluation can be complicated for the physician’s evaluation and further interpretation [8]. Objective determination of a patient’s physical and functional capacity is possible while using such a reliable and grounded method like the 6-minute walk test (6MWT) [9, 10]. The 6MWT is used as an alternative to the cardiopulmonary exercise testing for evaluating functional capacity depending on the patient’s capacity [11]. In clinical practice, the data on the wide use of cardiopulmonary exercise testing, treadmill test, or cardiac stress test is possible for using for some patients with decompensated HF, especially this applies to elderly patients with comorbid pathology [12]. The 6MWT is simple in daily use that does not require any special equipment [13] or additional involvement of medical staff to conduct it [14]. The postinfarction rehabilitation for the patients with decompensated HF is addressed to minimize this syndrome consequences and to improve the patient’s state that is defined as a non-drug therapy complex considering physical exercise program [15].

Despite that the 6MWT is used widely for evaluation of the patient’s functional state at HF, no trials studied changes in NT-proBNP during the dosed physical exercise in this patient population. The aim of the research is to determine the futility of NT-pro BNP level analysis during dosed physical exercise for diagnosing decompensated HF in the postinfarction period and the possibility to determine the HF functional class.

2. Materials and methods

The study was conducted basis of Regional Clinical Cardiology Center, infarction department No. 2 and rehabilitation during 2017–2020 years.

160 patients with previous MI were examined, patients’ average age was (56.67 ± 5.72) years. The patients were randomized in 2 groups dependently on the presence of the signs of II A-B according to V. Kh. Vasylenko and M. D. Strazhesko classification and FC III-IV (according to NYHA) decompensated chronic HF. Group I as the main group consisted of 120 patients with Q-QS and non-Q MI; group II (the control one) had 40 patients with MI without signs of decompensated HF; 20 healthy people made up a norm group. An inclusion criterion for the patients was Q-QS and non-Q MI occurring not earlier than before 28 days before the study. The examined groups were homogenous according to age, gender, disease severity, duration of the postinfarction period, the clinical manifestation of decompensation. The clinical diagnosis was made according to the European Society of Cardiology guidelines based on collecting anamnesis, physical examination, and data of laboratory-instrumental examination: general clinical analyses, electrocardiography, echocardiography, chest X-ray.

The members of the Ethics Commission (extract from protocol No. 5 dated January 13, 2016) at the Ivano-Frankivsk National Medical University, decided that this study would not contradict the main provisions of the GCP, Convention Council of Europe on human rights and biomedicine, the Helsinki Declaration of the World Medical Association on ethical principles for the conduct of scientific medical research with the participation of man and the Law of Ukraine «On Medicines». All patients signed an informed consent to participate in a clinical trial.

All patients performed the 6MWT, had evaluated their susceptibility to the test according to the Borg rating, had an ECG done in 12 standard leads to trace hemodynamic destabilization, an enzyme-linked immune-sorbent assay of NT-proBNP levels with the help of Dialogue Diagnostics LLC assay kits on the Cobas H 232 POC system by Roche Diagnostics. The 6 MWT was conducted in the morning, in the 30–50 m hospital corridor. Before the testing, the patient had breakfast, did not take any cardiology medications, did not smoke, and
limited his or her physical activity 2 hours before the start of the test. Before the walking, we recorded HR, BP (systolic and diastolic), and ECG in 12 standard leads [7].

Contraindications to the test with dosed physical activity were: unstable angina, myocardial infarction within a month, uncontrolled angina or arterial hypertension (SBP > 180 mmHg, DBP > 120 mmHg), HR < 50 or >120 bpm, musculoskeletal disorders, and other diseases which development can worsen due to physical exercise.

Criteria to stop the test were: chest pain, severe dyspnea, dizziness, wobbling when walking, sweating, sudden paleness, SpO2 less than 86 %. According to the results of the test, the distance traveled during 6 minutes (6MWD – 6 Minute Walking Distance) is measured in meters and compared to the normal ranges (6MWD). Also, the perceived exertion scale was evaluated.

Statistical analysis of received results was performed with the help of the STATISTICA-7 software package and the statistical function package in Microsoft Excel on a personal computer with using of variance statistical method. In the course of the work, we counted an arithmetic mean M, a standard deviation 6, a standard error in arithmetic mean m, number of variants (n), probability of the difference of the two arithmetic means p; the means $p \leq 0.05$ were evaluated as probable.

To compare the probability between the study groups about the presence of clinical signs and changes at physical examination, we used the F-test.

3. Research results

While evaluating the clinical course of MI, we determined distinct worsening of physical activity indices in the group of patients where MI was complicated with decompensated HF (Table 1).

So, ST depression was present in 67 (55.8 %) patients with past MI complicated with decompensated HF unlike the group of patients, who had Q-QS and non-Q MI without the signs of decompensated HF. Angina and dyspnea occurred in 80 (66.7 %) and 75 (62.5 %) cases in the second group of patients unlike the first one, where these signs were in 11 (27.5 %) and 13 (32.5 %) respectively.

Signs of coronary insufficiency such as dizziness and signs of poor peripheral perfusion (cyanosis/paleness) occurred in 104 (86.7 %) and 79 (65.8 %) cases that differ from the same values in the second group 4 (10.0 %) and 14 (35.0 %) respectively. 88 (73.3 %) patients with the signs of decompensated HF felt general weakness, fatigue, and expressed a request to stop the test.

As a result of analyzing the 6MWT, we found out that decompensated HF worsens significantly results of the test (Table 2).

So, the travelled distance in the patients of the third group was significantly lower and was $(174.32 \pm 2.65)$ m ($p \leq 0.05$) compared to the patients of the second and first groups where this index was $(383.75 \pm 5.75)$ m ($p \leq 0.05$) and $(573.97 \pm 4.51)$ m respectively.

Normal travelled distance decrease was accompanied by an inadequate hemodynamic response to physical exercises that was expressed in a disproportionate increase of HR, SBP, and DBP.

The HR in the postinfarction patients with the signs of decompensated HF was before the exercise $(88.2 \pm 3.18)$ bpm ($p \leq 0.05$); in the patients with past MI without the signs of decompensated HF, it was $(75.32 \pm 3.41)$ bpm ($p \leq 0.05$); and in the practically healthy people, it was $(77.73 \pm 3.02)$ bpm.

Table 1
Clinic signs of physical activity in patients in the postinfarction period dependently on the presence of decompensated HF

| Sign                | MI patients without decompensated HF ($n = 40$) | MI patients with decompensated HF ($n = 120$) |
|---------------------|-----------------------------------------------|-----------------------------------------------|
| ST depression       | 10 (25.0 %)                                   | 67 (55.8 %)*                                 |
| Angina              | 11 (27.5 %)                                   | 80 (66.7 %)*                                 |
| Dyspnea             | 13 (32.5 %)                                   | 75 (62.5 %)*                                 |
| Rhythm disorder     | 9 (22.5 %)                                    | 79 (65.8 %)*                                 |
| Dizziness           | 4 (10.0 %)                                    | 104 (86.7 %)*                                |
| Cyanosis/paleness   | 14 (35.0 %)                                   | 79 (65.8 %)*                                 |
| Fatigue             | 13 (32.5 %)                                   | 88 (73.3 %)*                                 |

Note: in brackets, there is a percent of the general number of patients in the group; $p$ is the probability of the difference between the group of patients with decompensated HF and the patients without decompensated HF; * $p < 0.05$
The HR after the exercise of stress test increased in all observed groups, its increase was practically the same, as in the patients with decompensated HF in the postinfarction period, as well as in ones without it: 19.46, and 19.25 respectively, compared to the healthy people where the HR increase after the dosed physical activity was 10.68.

SBP level at rest was in the third group (161.21 ± 7.02) mmHg (p ≤ 0.05) that was probably higher than the same value of the second and first groups (132.00 ± 8.14) mmHg (p < 0.05) and (122.03 ± 8.11) mmHg respectively.

After the 6MWT SBP value increased in the third examined group to (179.43 ± 6.02) mmHg (p ≤ 0.05) and in the second and first ones (150.38 ± 6.24) mmHg (p ≤ 0.05) and (129.03 ± 7.34) mmHg. The increase of values after the 6-minute walk test was 11.30, 13.92, and 5.74, respectively.

Similar patterns of increased DBP were observed especially after a physical exercise. So, in patients with decompensated HF in the early and late postinfarction period, this value increase was 11.10; in patients without the signs of decompensated HF, it was 11.17; and in healthy people, it was 7.19.

During the rating of individual perceived exertion, we observed significant feeling unwell in patients with past myocardial infarction complicated with decompensated HF (Table 3).

Fatigue, shortness of breath, chest pain during the physical exercise were evaluated in the group of patients where MI was complicated with decompensated HF as (8.70 ± 0.76) points, (3.60 ± 0.49) points, and (3.57 ± 0.58) points respectively that was significantly higher, than in the group of patients where MI was not complicated with decompensated HF; here these indices were evaluated as (4.33 ± 0.47) points (p < 0.05), (2.45 ± 0.64) points, and (2.38 ± 0.67) points.

The total points, with which the examined evaluated their feelings after the dosed physical exercise, were (18.04 ± 0.79) points (p < 0.05) in the third group, (11.95 ± 0.68) points (p < 0.05) in the second one, and (7.15 ± 0.75) points in the first group.

The patients that had decompensated HF after MI noted the significant difficulty in doing the 6MWT that manifested in significant muscle pain, shortness of breath, constantly tight chest, excessive sweating. NT-proBNP in the group of patients with MI and decompensated HF was (950.38 ± 3.15) pmol/L (p < 0.05); in patients with past MI without the signs of decompensated HF, it was (580.15 ± 3.03) pmol/L (p < 0.05) and in the practically healthy people, it was (111.20 ± 3.47) pmol/L (Table 4).

With the results of the performed 6MWT and NT-proBNP enzyme-linked immunosorbent assay in blood serum in the patients with decompensated HF that occurred after the MI, we performed a correlation analysis of the value of the exercise tolerance, namely covered distance by the patients in 6 minutes, and this marker concentration.

We found out a reverse moderate correlation between the distances that had been covered by a patient during the 6MWT NT-proBNP level in blood serum of examined patients. Correlation coefficient (r) between presented values was even (0.84) (p < 0.05).

### Table 2

| Value, measure unit | Healthy people (n = 40) | MI patients without decompensated HF (n = 40) | MI patients with decompensated HF (n = 120) |
|---------------------|------------------------|----------------------------------------------|--------------------------------------------|
| Normal distance, m  | 574.25 ± 6.25          | 565.00 ± 6.88*                              | 545.95 ± 5.62*                             |
| Travelled distance, m | 573.97 ± 4.51          | 383.75 ± 5.75*                              | 174.32 ± 2.65*                             |
| Heart rate at rest, bpm | 70.23 ± 6.37          | 75.32 ± 3.41*                               | 88.20 ± 3.18*                              |
| Heart rate after exercise, bpm | 77.73 ± 3.02          | 89.82 ± 2.98*                               | 105.37 ± 2.82*                             |
| SAT at rest, mmHg   | 122.03 ± 8.11          | 132.00 ± 8.14*                              | 161.21 ± 7.02*                             |
| SAT after exercise, mmHg | 129.03 ± 7.34        | 150.38 ± 6.24*                              | 179.43 ± 6.02*                             |
| DAT at rest, mmHg   | 78.57 ± 3.65           | 91.6 ± 3.59*                                | 92.78 ± 2.18*                              |
| DAT after exercise, mmHg | 84.22 ± 2.2           | 101.83 ± 2.11*                              | 103.08 ± 2.05*                             |

Note: probability of value difference: p1 – compared to healthy people; p2 – compared to patients without the signs of decompensated HF; * – p < 0.05

The correlation coefficient (r) between presented values was even (0.84) (p < 0.05).
Table 3
Rating of perceived exertion scale (Borg scale) in patients in postinfarction period dependently on decompensated HF

| Sign, points          | Healthy people (n = 40) | MI patients without decompensated HF (n = 40) | MI patients with decompensated HF CH (n = 120) |
|-----------------------|-------------------------|---------------------------------------------|---------------------------------------------|
| Fatigue               | 6.93±0.76               | 11.0±0.67*                                   | 17.84±0.64*                                 |
| Feeling               | 6.91±0.73               | 11.9±0.59*                                   | 17.74±0.76*                                 |
| Shortness of breath   | 0                       | 11.18±0.84*                                  | 17.94±0.67*                                 |
| Angina                | 0                       | 11.95±0.6*                                   | 18.04±0.79*                                 |
| Total points          | 6.92±0.01               | 11.51±0.49*                                  | 17.89±0.13*                                 |

Note: probability of value difference: p₁ – compared to healthy people; p₂ – compared to patients without the signs of decompensated HF; * – p < 0.05

Table 4
The level of NT-proBNP in the postinfarction period depending on the presence of decompensated CH

| Value, measure unit | Healthy people (n = 40) | MI patients without decompensated HF (n = 40) | MI patients with decompensated HF CH (n = 120) |
|---------------------|-------------------------|---------------------------------------------|---------------------------------------------|
| NT-proBNP pg/ml, before loading | 111.20±3.47          | 580.15±3.03                                 | 950.38±3.15                                 |
| NT-proBNP pg/ml, after loading | 116.20±4.83          | 619.03±4.70                                 | 1048.06±4.83                                |

Note: probability of value difference: p₁ – compared to healthy people; p₂ – compared to patients without the signs of decompensated HF; * – p < 0.05

Most patients with HF have a decrease in exercise tolerance. That is why tolerance to fasic activity is used to determine the degree of changes in myocardial contractility. High levels of NT-proBNP indicate an unfavourable prognosis. Therefore, inadequate response to dosed exercise and increased immunological parameters as quantitative markers of HF can be useful not only for diagnosis but also for risk stratification, decision-making to optimize the treatment of such a group of patients and the decision to discharge.

4. Discussion

The main finding of this study was revealing of absolute decrease in patient’s capacity to cover a normal distance during 6 minutes that was being accompanied by the probable increase of NT-proBNP level after the performed test with dosed physical exercise in patients with decompensated HF in the postinfarction period. Studies by Boman K. et al. [16] showed that increased NT-proBNP levels suggested the high mortality rate in patients with decompensated HF. NT-proBNP concentration in blood plasma is a strong biomarker of decompensated HF [17]. Natriuretic peptides have an important place among biomarkers which reflect pathophysiological mechanisms of development and decompensation of HF [18]; their analysis is most informative in patients with shortness of breath and suspected decompensated heart activity after Q-QS and non-Q wave MI [19]. Also, in acute and decompensated HF, increased NP levels are independent predictors of in-hospital mortality [18, 20], and the values of the so-called «grey zone» are associated with rather long-term consequences of this syndrome. Similar patterns in the change in NT-proBNP concentration were observed during performing this study too. As the data gotten from the Swedish Heart Failure Registry and presented by Savarese et al. showed higher NT-proBNP levels associating with cardiovascular events [21, 22], that was recorded during this study too, since exactly such values were independent predictors of decompensated HF in early and late postinfarction period. One more finding of this clinical study was correlation relevance between the distance which the patient covered during the 6MWT and NT-proBNP level in blood serum of examined patients. The 6MWT can be considered valuable for determining HF functional class from several sides. As this study as well as numerous other ones presented, the 6MWT is a test with physical exercise and reflects the patient’s capacity to perform daily exercises better, than the test with maximal physical exer-
cise [23, 24]. In our study the 6MWT was used for all patients, distance limits deferred for patients with postinfarction cardiolsclerosis dependently on decompensated HF.

**Study limitations.** A limitation of the study is the fact, that in a course, that in most patients with HF, exercise tolerance reduces and the 6 MWT is used to determine the degree of changes in myocardial contractility, it was found high levels of natriuretic peptide, which indicate an unfavourable prognosis. Therefore, an inadequate response to graded exercises and increase in the concentration of immunological indicators as quantitative markers of HF can be useful for diagnosis, as well as risk stratification, establishing functional class of HF.

**Prospects of the further research.** Since the main limits of changes in NT-pro BNP depends on the signs of decompensated HF secondary to acute MI have been determined, we plan to develop an algorithm for predicting the development of this syndrome in the post-infarction period under conditions of higher FC formation and assessing the quality of therapy, as well as determining the frequency and time periods of using these peptides for making therapeutic decisions.

5. **Conclusions**

1. The body response of the patient to dosed physical exercises and NT-proBNP levels has the biggest significance for clinical and prognostic evaluation of the postinfarction period complicated with decompensated HF. NT-proBNP in the group of patients with MI and decompensated HF was $(950.38 \pm 3.15)$ pmol/L ($p < 0.05$); in patients with past MI without the signs of decompensated HF, it was $(580.15 \pm 3.03)$ pmol/L ($p < 0.05$).

2. Inadequate response to dosed physical exercises and increased immunological parameters as quantitative HF markers can be useful not only for diagnostics but also for the risk stratification for decompensated HF that had occurred in patients on different rehabilitation stages after an acute MI, as well as the possibility to optimize and personalize further treatment tactics for this patient population.

**Conflicts of interest**

The authors declare that they have no conflicts of interest.

**Financing**

The study was performed without financial support.

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Prospects for NT-pro BNP level determining in physical activity conditions in patients during the rehabilitation period after the myocardial infarction, complicated with decompensated heart failure. EUREKA: Health Sciences, 5, 10–16. doi: http://doi.org/10.21303/2504-5679.2021.001793

Received date 21.06.2021
Accepted date 23.09.2021
Published date 30.09.2021

How to cite: Vakaliuk, I., Levandovska, Kh., Tymochko, N. (2021). Prospects for NT-pro BNP level determining in physical activity conditions in patients during the rehabilitation period after the myocardial infarction, complicated with decompensated heart failure. EUREKA: Health Sciences, 5, 10–16. doi: http://doi.org/10.21303/2504-5679.2021.001793