https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-2-3553

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# In-hospital changes of echocardiographic parameters and their relationship with the procollagen I C-terminal propeptide in patients with myocardial infarction and preserved left ventricle systolic function

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**Aim.** To study the changes of echocardiographic parameters and their relationship with the procollagen I C-terminal propeptide (PICP) during hospitalization of patients with ST-segment elevation myocardial infarction (STEMI) and preserved left ventricular (LV) systolic function.

**Material and methods.** A total of 120 (100%) patients hospitalized with STEMI were examined. Upon admission, all patients underwent standard examinations to verify myocardial infarction (MI), including coronary angiography and, if necessary, coronary stent implantation. The mean values of LV ejection fraction (LVEF) were 40-49% in 3 patients (2,5%), <40% — in 31 patients (26%), LVEF was. We also analyzed patients with LVEF ⩾50%, n=86 (71,6%); mean age was 57,8 years. During the hospitalization, all patients received standard therapy; on the 1st and 12th day of MI, the PICP levels in venous blood serum was determined by enzyme-linked immunosorbent assay. In order to compare PICP values, a control group of healthy volunteers n=20 (100%) was formed, which were comparable by gender and age. In this group, the concentration of PICP was 179,2 [163.5; 194.9] ng/ml.

**Results.** By the 12th day, a significant decrease in the following parameters of the transmitral flow was revealed: DT (p=0,049), dE (0,012), Em (0,029), Em/ Am (p=0,000), Em/ early mitral flow propagation velocity (Vp) (p=0,001). This indicates diastolic function deterioration. At the same time, by the end of hospitalization, systolic function deterioration was recorded in 15,1% of cases. Initially, a higher PICP on the 1st day relative to the control group tended to decrease the concentration by the 12th day, but the differences did not reach statistical significance (p=0,466). Correlation analysis showed a relationship between PICP and echocardiography (Tei index, p=0,026, and mitral annulus velocity, p=0,049).

**Conclusion.** At the hospital stage of treatment of patients with STEMI and preserved LVEF, a negative changes of echocardiography parameters characterizing diastolic dysfunction was revealed. Positive correlation was established between the concentration of PICP with mitral annulus velocity and the Tei index, indicating an association between myocardial fibrosis and diastolic dysfunction.

**Key words:** myocardial infarction, markers of fibrosis, diastolic dysfunction.

**Relationships and Activities:** not.

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**Received:** 09.10.2019
**Revision Received:** 09.11.2019
**Accepted:** 20.01.2020



**For citation:** Osokina A.V., Karetnikova V. N., Polikutina O. V., Ivanova A. V., Gruzdeva O. V., Ryzhenkova S. A., Artemova T. P., Barbarash O. L. In-hospital changes of echocardiographic parameters and their relationship with the procollagen I C-terminal propeptide in patients with myocardial infarction and preserved left ventricle systolic function. *Russian Journal of Cardiology*. 2020;25(2):3553 doi:10.15829/1560-4071-2020-2-3553

For many decades, cardiovascular diseases (CVD) have been one of the main causes of disability and high mortality among the working-age population [1-3]. In addition, the incidence of ST-segment elevation myocardial infarction (STEMI) increase among young population, more often men [4-6]. Heart failure (HF), as the most common late complication of myocardial infarction (MI), is increasingly progressing in patients with preserved myocardial contractility [7]. It was proved that during the first year after MI, mortality from left ventricular (LV) diastolic dysfunction (DD) ranges from 5-8%, and after 5 years, it is comparable with the mortality rate in patients with systolic HF [8]. LV myocardial fibrosis is considered as one of the most significant mechanisms for the development and progression of DD. Currently, much attention is paid to the study of serum markers of myocardial fibrosis, including collagen precursors. In particular, markers characterizing the activity of collagen synthesis and degradation are discussed [9]. Of particular note is procollagen I C-terminal propeptide (PICP) — precursor of type I collagen [10]. The issue remains open about the relationship of serum biomarkers of myocardial fibrosis with the echocardiographic parameters of cardiac structure, including after MI.

The aim of the study was to assess the changes of echocardiographic parameters and their relationship with the PICP during hospitalization of patients with STEMI and preserved LV systolic function.

## Material and methods

Using the continuous sampling method, we included 120 (100%) patients with STEMI hospitalized for emergency indications for 7 months of 2015. There were following inclusion criteria: 1) an established diagnosis of STEMI (European Society of Cardiology (2015); 2) signed informed consent; 3) age >18 years; 4) Killip class I-III acute HF. There were following exclusion criteria: 1) clinically meaningful concomitant pathology; 2) acute coronary syndrome (ACS) as a complication of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); 3) age ⩾80 years; 4) Killip class IV acute HF; 5) death on the first day of hospitalization. The mean age of the sample was 57,8 years. There were 75,8% (n=91) of men and 24,2% (n=29) of women. All women were postmenopausal. In the hospital, all patients underwent standard laboratory and instrumental examinations to verify MI. Upon admission, all patients underwent coronary angiography (CA) using the Innova 3100 cath/angio system (General Electric, USA) and, if necessary, coronary stent implantation.

Echocardiography was performed using the Sonos 2500 ultrasound system (Hewlett-Packard, USA) (Russian HF Society, Russian Society of Cardiology, Russian Scientific Medical Society of Internal Medicine Guidelines (2018) for HF: chronic and acute decompensated. Diagnosis, prevention and treatment). The following parameters were determined: end-diastolic volume (EDV), end-systolic volume (ESV), end-diastolic dimension (EDD), end-systolic dimension (ESD), left (LA) and right atrial (RA) sizes, general myocardial contractility, state of heart valves, LV wall thickness, the presence and extent of dyskinesia in the areas of necrosis and scarring, aneurysm, papillary muscle damage and myocardial rupture zones according to the standard technique using one-dimensional and two-dimensional echocardiography, pulsed and continuous-wave Doppler echocardiography. The LV ejection fraction was calculated as EF=(LVEDV–LVESV/LVEDV)×100% (Simpson's rule). For the diagnosis of DD, we assessed following parameters of transmitral flow: ratio of peak velocity filling in early diastole (E) to atrial peak velocity filling (A-N=0,22-0,32 ms) (E/A-N ratio ⩾1), isovolumic relaxation time (IVRT), deceleration time (DT) of early diastolic filling estimated by pulsed Doppler echocardiography (N=160-220ms), early diastolic mitral annular velocity (e'), — ratio of E-wave over e'-wave (E/e' ratio), LV IVRT (IVRT-N=70-90 ms). The Tei index was calculated as IVCT+IVRT/ET (normal rate in adults <0,4). Increased values of this parameter reflect reduced systolic function; Tei index >1,0 are a sign of severe systolic and diastolic dysfunction.

In the study sample, LVEF of 40-49% were determined in three patients (2,5%). In 26% (n=31) of patients, LVEF was <40%. The final analysis was performed in patients with LVEF ⩾50%, n=86 (71,6%).

We determined serum PICP levels on the 1$^{st}$ and the 12$^{th}$ days of hospitalization by enzyme-linked immunosorbent assay using BCM Diagnostics kits (USA). During hospitalization, all patients received standard therapy in accordance with ESC guidelines (2015).

In order to compare the values of the studied markers, we formed control group of healthy volunteers (n=20) with comparable age (mean age 57,9 years) and gender (15 men (75%), 5 women (25%)). In the control group, the concentration of PICP was 179,2 [163,5; 194,9] ng/ml. Table 1 presents the clinical and medical history of the study sample.

The age of the patients was 59 [52; 64] years. We revealed high prevalence of cardiovascular risk factors: ~1/2 of patients were smokers; >2/3 of patients had a long-standing hypertension (HTN). In addition, hypercholesterolemia (21,6%) and carbohydrate

**Table 1**

**Clinical characteristics of study patients**

| Parameter | n | % |
|---|---|---|
| Men | 63 | 73,2 |
| Women | 23 | 27,7 |
| Obesity (BMI ⩾30 kg/m$^2$) | 24 | 28 |
| Impaired carbohydrate metabolism | 15 | 17,4 |
| Current smoking | 38 | 44,2 |
| Former smoking | 4 | 4,6 |
| Hypertension | 61 | 70,9 |
| Hypercholesterolemia | 18 | 21 |
| Family history of coronary artery disease | 3 | 3,5 |
| Old myocardial infarction | 3 | 3,5 |
| Angina manifestations in history | 27 | 31,4 |
| Heart failure manifestations in history | 10 | 11,6 |
| Atrial fibrillation | 2 | 2,3 |
| Acute cerebrovascular accident (not earlier than 1 year before the study) | 4 | 4,6 |
| Peripheral artery disease | 1 | 1,2 |
| Chronic kidney disease | 2 | 2,3 |
| Percutaneous coronary intervention (not earlier than 1 year before the study) | 2 | 2,3 |

metabolism disorders (18%) were also quite common.

Statistical processing was carried out using the software package Statistica 6.0. Independent groups were compared using the Mann-Whitney U test; dependent groups — Wilcoxon signed-rank test. The dependence between variables was determined by the Spearman's rank correlation coefficient. The differences were considered statistically significant at $p<0,05$.

## Results

Echocardiography parameters on the 1st and 12th days were compared (Table 2). There was a significant increase of the LVEF ($p<0,001$) and LV stroke volume ($p<0,001$). At the same time, the ESD and ESV were decreased.

In a similar way, parameters of mitral flow were compared (Table 3). We revealed a significant decrease of following parameters: DT ($p=0,049$), dE (0,012), Em (0,029), Em/Am ($p<0,001$), Em/early mitral flow propagation velocity (Vp) ($p=0,001$).

On the 1st day, 25 (29,1%) patients with signs of DD were determined. On the 12th day, LVEF decrease <50% in 13 people (15,1%) and an increase in the number of patients with DD manifestations were identified.

There was a slight decrease in PICP levels on day 12 compared to day 1, however, the identified differences were not significant: 1st day — 605,0 (560,0; 670,0), 12th day — 602,0 (598,0; 625,0) ($p=0,466$). These values were significantly higher than in the control group (Figure 1).

Correlation analysis did not reveal the relationship between generally accepted echocardiographic parameters of LV diastolic function and PICP. Nevertheless, a relationship was found between PICP and echocardiographic parameters (Tei index and mitral annulus velocity), which can also characterize LV diastolic function (Figure 2). However, a direct comparison of the values of the Tei index and mitral annulus velocity by the 1st and 12th days did not revealed significant differences.

Figure 2 shows that PICP concentration on the 1st of MI has statistically significant positive correlation with the Tei index ($p=0,026$) and mitral annulus velocity ($p=0,049$). On the 12th day, such findings were not established.

## Discussion

The practitioners often contact with HF patients. Previously, this syndrome was considered as a consequence of impaired LV contractility. However, for several decades, systolic and diastolic dysfunctions are considered interconnected links of one global process — pathological cardiac remodeling [11]. In this study, we did not obtain the expected significant relationships between standard parameters revealing LVDD. However, we found relationship between other echocardiographic parameters (Tei index and mitral annulus velocity) and serum PICP levels [12].

There is much literature data that confirm the association of Tei index with HF class, increased in-hospital risk of sudden death, acute HF, arrhythmias, and early post-infarction angina. Tei index can be used to assess LV systolic function [12]. It is also significant for assessing the severity of LVDD. The estimation of the Tei index was proposed by Chuwa Tei in 1995 as a noninvasive Doppler-derived myocardial performance index. The limitation of this method is the technical difficulty of the simultaneous correct visualization. In addition to the technical difficulty, obtained results are affected by parameters such as heart rate and cardiac output. All of the above aspects significantly limit the practical application of this technique [13].

It should be noted that since the introduction of this parameter into clinical practice, studies have proved its more significant value for predicting long-term cardiovascular mortality after MI com-

**Table 2**

**Comparison of echocardiographic parameters during hospitalization**

| Parameter | 1st day of hospitalization Me [$Q_{25;}$ $Q_{75}$] | 12th day of hospitalization Me [$Q_{25;}$ $Q_{75}$] | p |
|---|---|---|---|
| Left ventricular ejection fraction, % | 59,0 [54,0; 63] | 62,0 [56,0; 65,0] | <0,0001 |
| End diastolic dimension (cm) | 5,35 [5,1; 5,6] | 5,4 [5,1; 5,6] | 0,9463 |
| End systolic dimension (cm) | 3,7 [3,5; 3,9] | 3,6 [3,4; 3,9] | <0,0001 |
| End diastolic volume (ml) | 135,0 [124,0; 154,0] | 135,0 [124,0; 154,0] | 0,8190 |
| End systolic volume (ml) | 58,0 [51,0; 66,0] | 54,0 [47,0; 66,0] | <0,0001 |
| Left atrium (cm) | 4,0 [3,9; 4,2] | 4,0 [3,9; 4,3] | 0,8128 |
| Right atrium (cm) | 4,1 [3,9; 4,4] | 4,2 [4,0; 4,4] | 0,3491 |
| Right ventricle (cm) | 1,8 [1,8; 1,8] | 1,8 [1,8; 1,8] | 0,4226 |
| Interventricular septum (cm) | 1,1 [1,0; 1,2] | 1,1 [1,0; 1,2] | 0,1614 |
| Left ventricular posterior wall (cm) | 1,1 [1,0; 1,2] | 1,1 [1,0; 1,2] | 0,1614 |
| Aorta (cm) | 3,5 [3,3; 3,6] | 3,5 [3,4; 3,6] | 0,0806 |
| End diastolic index (ml/$m^2$) | 68,0 [64,0; 79,0] | 70,0 [65,0; 81,5] | 0,7794 |
| End systolic index (ml/$m^2$) | 31,0 [25,0; 38,0] | 27,5 [23,5; 34,0] | 0,1000 |
| Stroke volume (ml) | 80,0 [73,0; 90,0] | 84,0 [77,0; 92,0] | <0,0001 |
| Myocardial mass (g) | 234,0 [206,0; 264,0] | 233,0 [206,0; 264,0] | 0,2488 |
| Myocardial mass index (g/$m^2$) | 130,0 [102,0; 142,0] | 125,0 [111,0; 140,0] | 0,2048 |

**Table 3**

**Comparison of mitral flow parameters assessed by Doppler echocardiography during hospitalization**

| Parameter | 1st day of hospitalization | 12th day of hospitalization | p |
|---|---|---|---|
| E (cm/s) | 57,0 [50,0; 70,0] | 60,0 [49,0; 73,0] | 0,6784 |
| A (cm/s) | 70,0 [60,0; 79,0] | 70,0 [58,0; 80,0] | 0,6051 |
| E/A | 0,80 [0,71; 1,22] | 0,79 [0,68; 1,21] | 0,9869 |
| IVRT (ms) | 111,0 [104,0; 118,0] | 106,0 [104,0; 118,0] | 0,1298 |
| IVRT (ms) | 107,0 [104,0; 118,0] | 106,0 [104,0; 118,0] | 0,2310 |
| DT(ms) | 196,0 [170,0; 224,0] | 189,5 [170,0; 222,0] | 0,0494 |
| AT (ms) | 124,0 [111,0; 141,0] | 131,0 [111,0; 137,0] | 0,4603 |
| ET (ms) | 294,0 [280,0; 313] | 287,0 [268,0; 303,0] | 0,1386 |
| dE (ms) | 242,0 [222,0; 274,0] | 238,0 [204,0; 272,5] | 0,0124 |
| dA (ms) | 157,0 [132,0; 176,0] | 157,0 [132,0; 176,0] | 0,5720 |
| IVCT (ms) | 91,0 [85,0; 98,0] | 90,0 [83,0; 97,0] | 0,0128 |
| Diastolic stiffness | 0,073 [0,060; 0,085] | 0,071 [0,060; 0,080] | 0,0533 |
| Em | 7,0 [6,0; 8,0] | 6,0 [5,0; 8,0] | 0,0290 |
| Am | 8,0 [6,9; 9,0] | 8,0 [7,0; 9,0] | 0,2578 |
| Em/Am | 0,83 [0,71; 1,17] | 0,75 [0,67; 1,12] | 0,0003 |
| E/Em | 8,8 [7,6; 11,4] | 9,0 [7,5; 10,43] | 0,0838 |
| Early mitral flow propagation velocity (sm/s) | 41,0 [34,0; 48,0] | 42,0 [35,0; 51,0] | 0,0000 |
| Em/early mitral flow propagation velocity | 1,5 [1,13; 2,0] | 1,3 [0,98; 1,84] | 0,0015 |
| Tei index | 0,70 [0,64; 0,75] | 0,69 [0,65; 0,78] | 0,552 |
| Mitral annulus velocity | 7 [6; 8] | 7 [6; 8] | 0,944 |

pared with the E/A ratio and the LV wall motion score index. However, there is a little information about the relationship of serum fibrosis markers and echocardiographic parameters of DD. Of particular interest in such combinations is due to the steady increase in the number of patients with HF with preserved ejection fraction (HFpEF) [7]. The aim of such studies is to search for a significant marker for determining individual strategy of management and timely therapy change in patients with risk of HF progression, despite the preserved LV contractility [14].

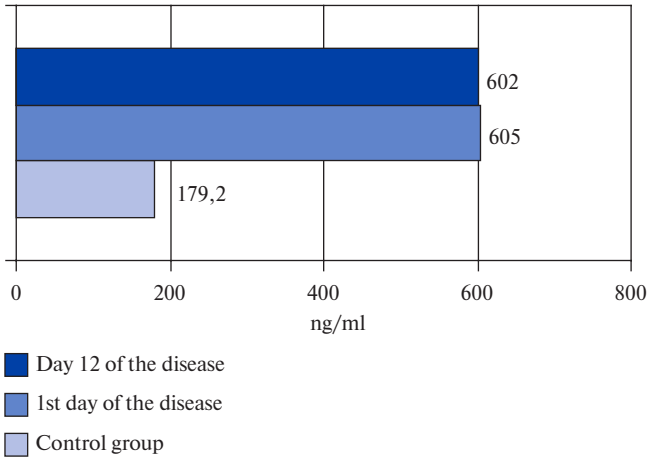


**Figure 1.** The changes of PICP in comparison with the control group during hospitalization.

The practical introduction of tissue Doppler imaging made it possible to evaluate the systolic velocity and amplitude of atrioventricular annular motion. One of the informative methods for analyzing LV myocardial function is assessing of mitral annular motion, most often — its lateral edge. According to the literature data, there are differences in the normative values of velocity parameters. Nevertheless, some studies have shown that tissue Doppler imaging of the mitral annulus provides the most detailed and accurate picture of the LV diastolic function than the standard parameters of mitral flow. It was established that with E-wave decrease and A-wave increase, DD deteriorates. The relationship of these parameters with the LVEF has been proven. The study by Naumenko EP, et al. (2014) revealed that peak systolic mitral annulus velocity (S') in patients with HFpEF is higher than in patients with systolic dysfunction, but less than in individuals without HF. This indicates subclinical systolic dysfunction. The peak S' $\geqslant$10 cm/s, estimated by spectral tissue Doppler imaging, make it possible to distinguish satisfactory LV contractility from reduced. The combination of E' decrease <8,5 cm/s and the E/A ratio <1,0 indicates pseudonormal mitral flow (sensitivity — 88%, specificity — 67%).

The present study revealed significant correlation of mitral annulus velocity and Tei index with PICP concentration on the 1st day of MI. It was proved that PICP, a type I collagen precursor, is characterized by large diameter fibers and numerous cross-links. It is

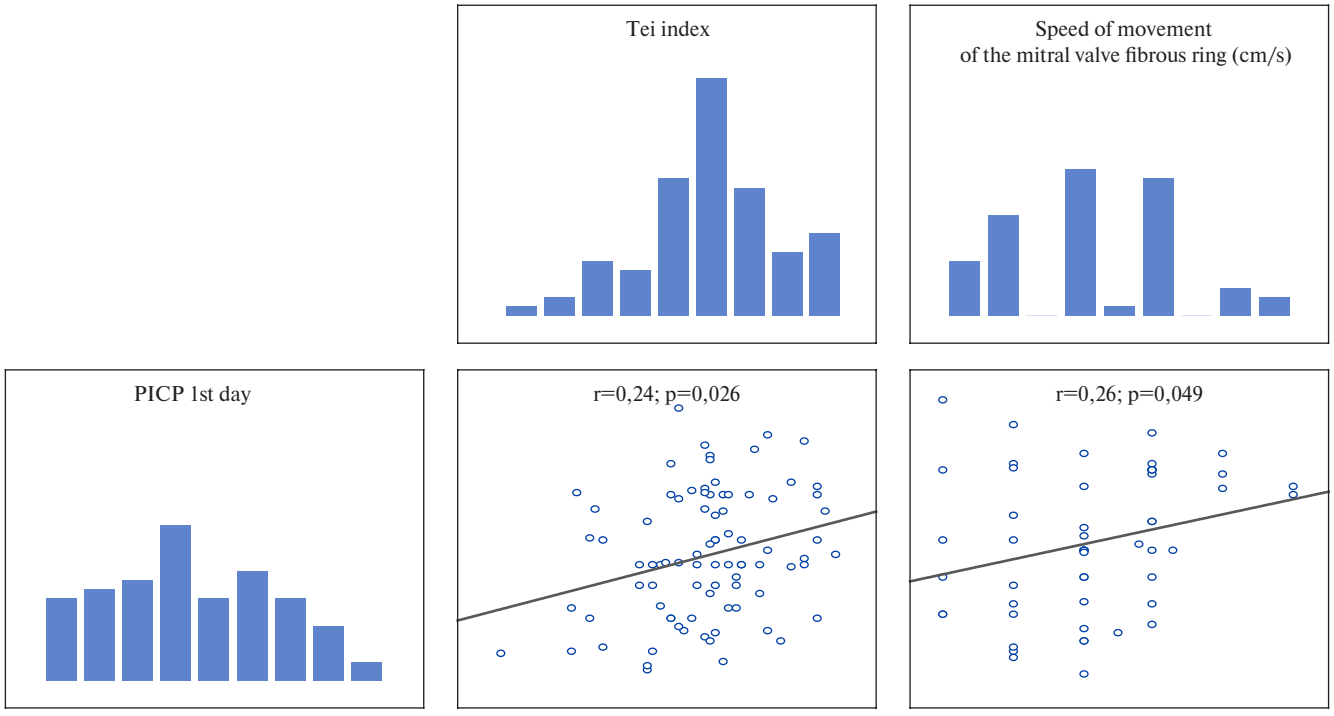


**Figure 2.** Correlation between PICP and echocardiographic parameters.

PICP that is associated with diffuse myocardial fibrosis, which is characterized by most unfavorable prognosis in HF patients [15].

Assessment of echocardiographic parameters during hospitalization revealed LVEF decrease <50% in 13 patients. We observed an increase in the number of ultrasound parameters with values indicating the LVDD deterioration. It is important that there were no clinical manifestations of HF aggravation during hospitalization. Perhaps these negative changes are the initial manifestation of impaired myocardial relaxation. It is at this stage that is important to identify patients who have a potential risk of HFpEF.

**Study limitation:** the analysis of peripheral serum biomarkers does not have 100% specificity and is inferior to the morphological diagnosis of fibrosis, namely the determination of the collagen volume fraction (biopsy).

## Conclusion

During hospitalization of patients with STEMI and preserved LVEF, an increase in the proportion of subjects with DD and some impairment of systolic function were found. Positive correlation was established between the concentration of PICP with mitral annulus velocity and the Tei index, indicating an association between myocardial fibrosis and DD.

**Relationships and Activities:** not.

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