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# Прогностическое значение изменений коронарного кровотока у пациентов с сохраненной фракцией выброса

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***Обоснование.*** Измерение фракции выброса при эхокардиографическом исследовании позволяет оценить глобальную сократимость левого желудочка. Снижение данного показателя свидетельствует о неблагоприятном прогнозе у пациентов, а в диапазоне нормальных значений этот параметр теряет свою прогностическую значимость. Для пациентов с нормальной фракцией выброса необходима разработка других прогностических методов.

***Цель исследования*** — изучить влияние изменений параметров коронарного кровотока, измеренных при помощи допплерографического исследования, у пациентов с сохраненной фракцией выброса левого желудочка в прогнозировании неблагоприятных исходов в течение года.

***Материалы и методы.*** В проспективное исследование включали пациентов, направленных на эхокардиографию в 2019–2020 гг. и наблюдавшихся в Санкт-Петербургском научно-исследовательском кардиологическом центре «Медика». Критерием включения был возраст старше 18 лет, критерием исключения — снижение фракции выброса левого желудочка менее 53 %. Помимо стандартной эхокардиографии использовали допплерографию для исследования скоростных показателей кровотока в коронарных артериях. Срок наблюдения составил 1 год. В исследуемую подгруппу пациентов вошли 453 человека.

***Результаты.*** За год наблюдения произошло 89 случаев спонтанных неблагоприятных событий, таких как смерть, инфаркт миокарда, нарастающая сердечная недостаточность, в том числе 19 летальных исходов. Умершие пациенты были старше выживших (средний возраст составил 76,6 ± 8,6 против 59,3 ± 15,5 лет; $p < 0,000001$), обладали меньшей глобальной продольной функцией (–13,8 ± 4,3 против –18,3 ± 3,6 %; $p < 0,000001$), большим индексом объема левого предсердия (54,6 ± 15,5 против 36,5 ± 13,1 мл/м$^2$; $p < 0,000000$), большим давлением в легочной артерии (39,5 ± 14,7 против 29,5 ± 8,1 мм рт. ст.; $p < 0,000000$), большим индексом массы миокарда левого желудочка (108,7 ± 37,2 против 88,1 ± 24,1 г/м$^2$, $p < 0,000000$) и нарушением диастолической функции [отношением скорости кровотока через митральный клапан в первую (раннюю) фазу наполнения левого желудочка и усредненной скорости движения фиброзного кольца митрального клапана 13,6 ± 7,1 против 9,4 ± 4,4; $p < 0,000000$], а также достоверно большей скоростью кровотока в передней межжелудочковой артерии (78,0 ± 39,0 против 50,0 ± 25,4 см/с; $p < 0,000007$). Только возраст и скорость кровотока в передней межжелудочковой артерии были независимыми предикторами смерти и инфаркта миокарда ($p < 0,004$).

***Заключение.*** Скоростные показатели кровотока в передней межжелудочковой артерии являются значимым прогностическим параметром краткосрочных спонтанных событий, включая смерть, у пациентов с сохраненной фракцией выброса.

**Ключевые слова:** фракция выброса; сохраненная фракция выброса; коронарные артерии; коронарный кровоток; скорость коронарного кровотока; эхокардиография.

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# Prognostic value of changes in coronary blood flow in patients with preserved ejection fraction

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***BACKGROUND:*** The measurement of the left ventricular ejection fraction during at echocardiographic study evaluates global contractility. A decrease in this parameter indicates a poor prognosis. However, in the range of normal values, the left ventricular ejection fraction loses prognostic significance. This category of patients requires the development of other prognostic methods.

***AIM:*** To explore the effect of changes in coronary blood flow parameters measured using dopplerography in patients with preserved left ventricular ejection fraction in predicting adverse outcomes over the next year.

***MATERIALS AND METHODS:*** The prospective study included patients referred for echocardiography in 2019–2020 followed up at the Saint Petersburg Research Center of Cardiology "Medika". The inclusion criterion was age over 18 years. A decrease in left ventricular ejection fraction of less than 53% was an exclusion critrion. In addition to standard echocardiography, dopplerography has been used to study the velocity parameters of blood flow in the coronary arteries. The observation period was 1 year.

***RESULTS:*** The control group included 453 patients. During the year of observation, 89 cases of spontaneous adverse events (death / myocardial infarction / progressive heart failure) occurred, including 19 deaths. The patients who died were older (76.6 ± 8.6 vs. 59.3 ± 15.5 years; $p < 0.000001$), with lower global longitudinal function (–13.8 ± 4.3% vs. –18.3 ± 3.6%, $p < 0.000001$), with a large volume index of the left atrium (54.6 ± 15.5 vs. 36.5 ± 13.1 ml/m$^2$; $p < 0.000000$), high pressure in the pulmonary artery (39 ± 14.7 vs. 29.5 ± 8.1 mmHg; $p < 0.000000$), high left ventricular myocardial mass index (108.7 ± 37.2 vs. 88,1 ± 24.1 g/m$^2$, $p < 0.000000$) and impaired diastolic function [the ratio of blood flow velocity through the mitral valve in the first (early) phase of left ventricular filling and the average velocity of the mitral valve fibrous ring 13.6 ± 7.1 vs. 9.4 ± 4.4; $p < 0.000000$]. The blood flow velocity in the anterior interventricular artery was significantly higher (78.0 ± 39.0 vs. 50.0 ± 25.4 cm/s, $p < 0.000007$). Only age and flow velocity in anterior interventricular artery were independent predictors of death / myocardial infarction ($p < 0.004$).

***CONCLUSIONS:*** Velocity parameters in the anterior interventricular artery are a significant predictor of short-term spontaneous events, including death, in patients with preserved ejection fraction.

**Keywords:** ejection fraction; preserved ejection fraction; coronary artery; coronary flow; coronary flow velocity; echocardiography.

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## BACKGROUND

Currently, left ventricular ejection fraction is one of the main parameters measured during routine echocardiography. Left ventricular contractility is widely assessed to diagnose heart failure. A decrease in this parameter indicates an unfavorable patient prognosis. However, the prognostic accuracy of ejection fraction seriously decreases even within the range of normal values [1]. Earlier studies with coronary blood flow assessment using color and pulsed-wave Doppler imaging have been published, showing the significance of this parameter in the prediction and diagnosis of adverse cardiovascular events [2–4]. The authors of the present study have already noted the additional prognostic value of coronary blood flow velocity and determined the joint influence of the left ventricular contractility and left ventricular ejection fraction on the risk of adverse cardiovascular events in different patient groups [6].

**This study aimed** to evaluate the significance of changes in coronary blood flow parameters measured by Doppler in patients with preserved left ventricular ejection fraction in predicting adverse outcomes during the year.

## MATERIALS AND METHODS

The prospective, single-center cohort study from April 2019 to March 2020 included all patients referred for echocardiography who were subsequently followed up at the Saint Petersburg Research Center of Cardiology "Medika." Inclusion criteria were >18-year-old patients and those who provided informed consent to participate in the study. The exclusion criteria were as follows:

- Decreased left ventricular ejection fraction of <53%
- Hemodynamically significant valve pathology
- A life expectancy of <1 year for comorbid and polymorbid pathologies, such as cancer, end-stage renal or hepatic failure, and severe obstructive pulmonary disease

Standard examination and questioning were performed to determine the anamnesis of patients.

*Echocardiography* was performed following the recommended standard technique [5].

*Coronary blood flow parameters* were *assessed* with an additional coronary tab and special settings to visualize coronary artery segments on Vivid 7 Dimension and Vivid E9 GE devices using M4S and M5S-D sector sensors. The standard and modified parasternal positions along the short and long axes from the second or third intercostal space were used to locate the coronary arteries.

To visualize the left coronary artery trunk, a normal antegrade blood flow in red or blue (red was detected by flow directed to the transducer, and blue was from the transducer) was determined using color Doppler imaging in the area of the left coronary sinus depending on anatomical features of

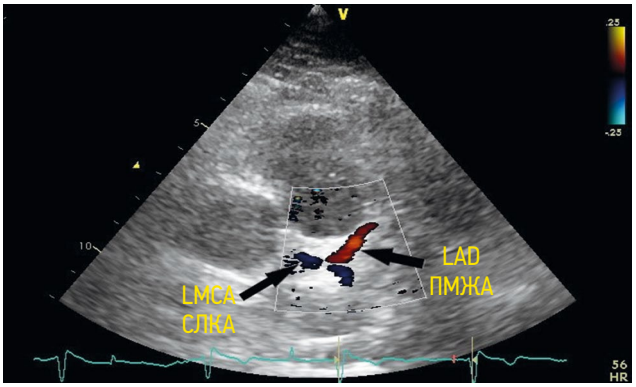


**Fig. 1.** Vizualization of the left main coronary artery from a modified left parasternal position along the long axis. LMCA — left main coronary artery; LAD — left anterior descending artery

**Рис. 1.** Визуализация ствола левой коронарной артерии из модифицированной левой парастернальной позиции по длинной оси. СЛКА — ствол левой коронарной артерии; ПМЖА — передняя межжелудочковая артерия

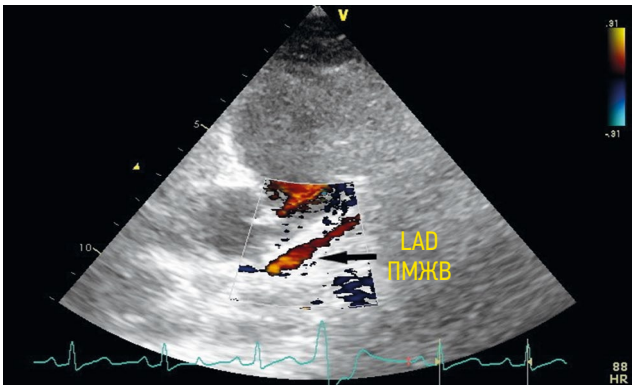


**Fig. 2.** Visualization of the anterior interventricular branch from a modified left parasternal position. LAD — left anterior descending artery

**Рис. 2.** Визуализация передней межжелудочковой артерии из модифицированной левой парастернальной позиции. ПМЖА — передняя межжелудочковая артерия

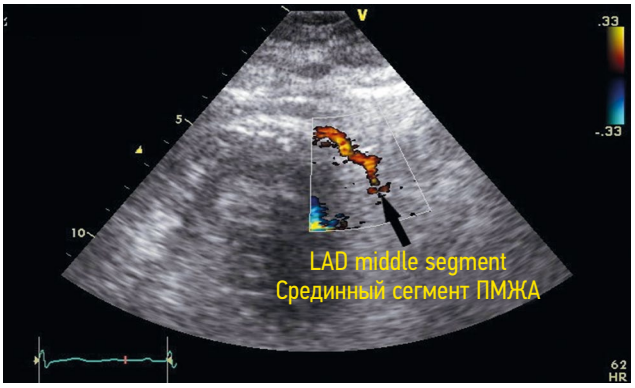


**Fig. 3.** Visualization of the anterior interventricular branch middle segment from a modified short-axis parasternal position in the anterior interventricular sulcus. LAD — left anterior descending artery

**Рис. 3.** Визуализация срединного сегмента передней межжелудочковой артерии из модифицированной парастернальной позиции по короткой оси в передней межжелудочковой борозде. ПМЖА — передняя межжелудочковая артерия

the chest, transducer position, and left coronary artery origin (Figure 1).

The left anterior descending (LAD) artery was visualized based on the following anatomical features: the anterior interventricular sulcus, the initial origin of the first diagonal artery, and the papillary muscles. A normal antegrade red blood flow was determined by color Doppler imaging. The proximal segment of the LAD was visualized by slightly changing the image plane in the modified left parasternal position along the short or long axis (Figure 2).

The midline LAD segment was visualized from the third or fifth intercostal space in the inferior left parasternal and the modified parasternal positions along the short or long axis of the left ventricle in the anterior interventricular sulcus and the modified apical tricuspid position (Figure 3).

To *quantify the blood flow in the coronary arteries*, its peak diastolic velocity was measured by point-finding. Values >65 cm/c were considered a significant increase in velocity.

*Left ventricular ejection fraction* was calculated using the Simpson method: the left ventricular volume was measured at the end of diastole and systole in two orthogonal apex positions (two-chamber and four-chamber) using the following formula:

$$EF = (EDV - ESV) / ESV,$$

where EF is the left ventricular ejection fraction, EDV is the end-diastolic volume, and ESV is the end-systolic volume.

Patients were followed up for 1 year after echocardiography. The study end-points were death from any cause and the cumulative point of all adverse outcomes, such as death, myocardial infarction, and increasing heart failure.

Statistical data processing was performed using STATISTICA 10.0 (Stat Soft Inc., USA) and MedCalc Statistical Software 14.8.1 (MedCalc Software bvba, Belgium). Qualitative data are presented as the occurrence in the cohort in percentages with a 95% confidence interval (CI), whereas quantitative data are presented as means and standard deviations or medians with 25% and 75% quartiles with minimum and maximum values depending on distribution normality. Continuous values were compared between the groups using Student's paired *t*-test. The critical significance level of the null statistical hypothesis was $p < 0.05$.

## RESULTS

The total number of patients included in the study was 581. Among them, 128 patients were excluded: 47 due to inaccessibility of the coronary artery imaging, 37 due to the absence of feedback, and 44 due to low left ventricular ejection fraction. Finally, the study subgroup comprised 453 patients. The allocation of this subgroup is shown in Figure 4.

The general characteristics of patients are presented in Table 1.

Patients with arterial hypertension predominated in the study subgroup of patients, whereas patients with diabetes mellitus and known coronary heart disease were significantly fewer.

Echocardiographic data of patients with preserved ejection fraction are presented in Table 2.

At 1 year after echocardiography, the cumulative end-points of death, myocardial infarction, and increasing heart failure were reached in 89 patients, including 19 deaths.

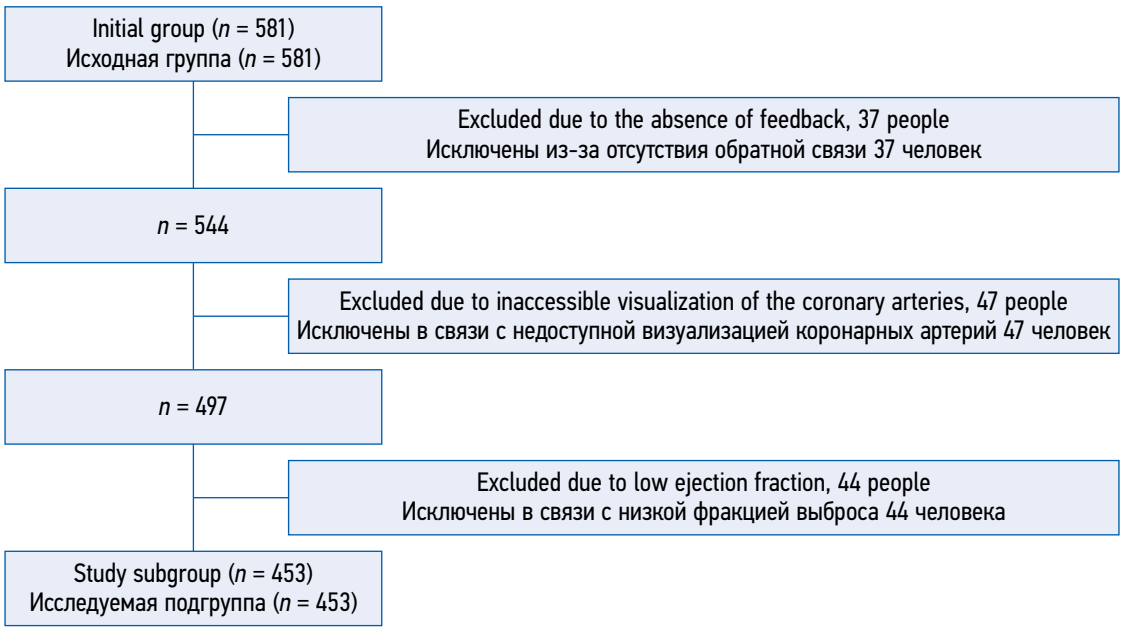


**Fig. 4.** Selection of patients for the study

**Рис. 4.** Выделение исследуемой подгруппы

### *Comparison of the rates of death and survival in patients with a normal ejection fraction*

When comparing the data of deceased patients and survivors, the mean age was higher (76.6 ± 8.6 vs. 59.3 ± 15.5 years; $p < 0.000001$), and no patients had diabetes mellitus (12% vs. 3.1%; $p < 0.001$).

In an analysis of echocardiographic parameters, a lower left ventricular end-diastolic volume (84.2 ± 21.1 vs. 95.7 ± 25.5 mL/m$^2$; $p < 0.04$) was observed in the cohort of patients who died compared to those who survived and global longitudinal left ventricular function (–13.8 ± 4.3 vs. –18.3 ± 3.6 %; $p < 0.000001$); higher left atrial volume index (54.6 ± 15.5 vs. 36.5 ± 13.1 ml/m$^2$; $p < 0.000000$), pulmonary artery pressure (45.7 ± 15.5 vs. 30.8 ± 9.7 mm Hg; $p < 0.000000$), and left ventricular myocardial mass index (112.2 ± 34.0 vs. 90.8 ± 20.3 g/m$^2$; $p < 0.001$); and worse diastolic function values due to the blood flow velocity to the mitral valve ratio during the first (early) phase of left ventricular filling and averaged mitral valve fibrous ring velocity (*E/e'*) (16.0 ± 5.8 vs. 9.9 ± 5.0; $p < 0.000003$).

Blood flow velocities in the proximal (78.0 ± 39.0 vs. 50.0 ± 25.4 cm/s; $p < 0.000007$) and median (57.7 ± 22.1 cm/s vs. 42.8 ± 20.3 cm/s; $p < 0.01$) LAD segments of patients who died with normal ejection fraction were higher than in those who survived.

### *Comparison of patients with normal ejection fraction with and without achieving the summary end-point such as death, myocardial infarction, and increasing heart failure*

In the group of patients with preserved ejection fraction with cumulative end-point attainment compared with patients without cumulative end-point attainment, the mean age (70.7 ± 10.8 vs. 57.5 ± 15.5 years; $p < 0.000000$), body mass index (29.8 ± 6.5 kg/m$^2$ vs. 27.5 ± 5.2 kg/m$^2$; $p < 0.0001$), systolic blood pressure (143.3 ± 19.3 vs. 135 ± 20.8 mm Hg St; $p < 0.0006$), and SCORE index (32.6 ± 18.8 vs. 13.8 ± 16.1; $p < 0.000000$) were higher. Patients with a history of adverse events were more likely to have arterial hypertension (21.7% vs. 9%; $p < 0.003$), diabetes mellitus (31% vs. 17.1%; $p < 0.01$), myocardial infarction (39.3% vs. 17.8%; $p < 0.004$)., and coronary artery stenting (37.8% vs 17.4%; $p < 0.002$).

Analysis of echocardiographic parameters in patients who reached compared with those who did not reach the cumulative end-point had reduced global longitudinal left ventricular function (–15.6 ± 4.2 vs. –18.6 ± 3.4; $p < 0.000000$) but had elevated myocardial contractility impairment index at rest (1.06 vs. 1.00; $p < 0.000000$), left atrial volume (86.8 ± 28.3 vs. 68.2 ± 27.6 ml; $p < 0.000000$), left atrial volume index (45.2 ± 13.2 vs. 35.5 ± 13.1 mL/m$^2$; $p < 0.00000$), pulmonary artery pressure (39.5 ± 14.7 vs. 29.5 ± 8.1 mm Hg Std, $p < 0.000000$), and myocardial mass

**Table 1.** Clinical findings of the study population (*n* = 453)
**Таблица 1.** Данные анамнеза пациентов (*n* = 453)

| Parameter | Value |
|---|---|
| Age, M ± SD, years | 60.2 ± 15.5 |
| Ratio by gender (male/female) | 176/277 |
| Body mass index, M ± SD, kg/m$^2$ | 27.9 ± 5.6 |
| Body surface area, M ± SD, m$^2$ | 1.9 ± 0.2 |
| Diabetes mellitus, *n* (%) | 56 (12.3) |
| Arterial hypertension, *n* (%) | 361 (79.7) |
| Myocardial infarction, *n* (%) | 27 (5.9) |
| Coronary artery stenting, *n* (%) | 37 (8.1) |
| Smoking status: | |
| • Smoker, *n* (%) | 33 (7.3) |
| • Former smoker, *n* (%) | 77 (17) |
| Sternum pain: | |
| • Typical angina pectoris, *n* (%) | 34 (7.5) |
| • Atypical angina pectoris, *n* (%) | 55 (12.1) |
| • Non-anginal chest pain, *n* (%) | 130 (28.7) |
| Heart rhythm: | |
| • Sinus rhythm, *n* (%) | 401 (88.5) |
| • Atrial fibrillation, *n* (%) | 44 (9.7) |
| • Permanent pacemaker rhythm, *n* (%) | 8 (1.8) |

*Note.* M, mean value; SD, standard deviation.

**Table 2.** Echocardiographic findings of the study population (*n* = 453)
**Таблица 2.** Эхокардиографические данные пациентов (*n* = 453)

| Parameter | Value |
|---|---|
| Heart rate, per min | 71.1 ± 15.6 |
| Left ventricular end-diastolic volume, ml | 95.9 ± 25.8 |
| Left ventricular end-systolic volume, ml | 33 ± 11.8 |
| Left ventricular end-diastolic volume index, ml/m$^2$ | 49.8 ± 11.2 |
| Left atrial volume, ml | 72.4 ± 27.8 |
| Left atrial volume index, ml/m$^2$ | 37.7 ± 13.1 |
| Pulmonary artery pressure, mm Hg | 31.4 ± 9.8 |
| Left ventricular ejection fraction, % | 65.8 ± 5.9 |
| Left ventricular contractility index | 1.01 ± 0.08 |
| Global longitudinal left ventricular function, % | –18.1 ± 3.7 |
| Diastolic function | 10.1 ± 5.2 |
| Myocardial mass index, g/m$^2$ | 92.8 ± 28.2 |

*Note.* Data are presented as mean values and standard deviations.

index (108.7 ± 37.2 vs. 88.1 ± 24.1 g/m$^2$, $p < 0.000000$), and a worse diastolic *E/e'* value (–13.6 ± 7.1 vs. –9.4 ± 4.4; $p < 0.000000$) was observed.

Blood flow velocity in the proximal and median LAD segments in patients who reached compared with those who did not reach the total end-point was on average significantly higher and was 73.8 ± 36.0 versus 45.1 ± 19.7 cm/s ($p < 0.000000$) in the proximal and 57.6 ± 27.6 versus 39.9 ± 16.5 cm/s ($p < 0.000000$) in the median segments.

***Multivariate analysis of parameters in the subgroup of patients with a preserved ejection fraction***

Multivariate analysis revealed that independent predictors for mortality included age (hazard ratio [HR] 1.08; 95% CI 1.01–1.15; $p < 0.03$) and maximum proximal LAD blood flow (HR 1.02; 95% CI 1.01–1.04; $p < 0.004$). Independent predictors of all adverse outcomes were age (HR 1.05, 95% CI 1.02–1.07; $p < 0.0007$), the presence of arterial hypertension (HR 2.77, 95% CI 1.15–6.67; $p < 0.03$), left ventricular global longitudinal strain value (HR 0.92, 95% CI 0.86–0.99; $p < 0.02$), myocardial mass index (HR 1.01, 95% CI 1.00–1.02; $p < 0.03$), and blood flow velocity in proximal segments of the left coronary artery (HR 1.02, 95% CI 1.01–1.03; $p < 0.0002$).

# DISCUSSION

We obtained data showing that changes in coronary blood flow velocity indices are a significant prognostic parameter of short-term spontaneous adverse events in patients with preserved ejection fraction. Short-term events were those that occurred within a year, whereas spontaneous events were death, myocardial infarction, and increasing heart failure. Previously, one study, described in the international medical literature, which analyzed the prognostic role of velocity parameters of coronary blood flow during echocardiography, has already been conducted and reported that a higher velocity in proximal segments of the left coronary artery provides prognostic information for detecting cardiac and overall mortality, besides basic echocardiographic parameters associated with known or suspected heart disease [7]. However, the conclusion of this work has several limitations because of its retrospective design. Similar data were obtained with magnetic resonance imaging, and high velocities in the arteries were found to affect the prognosis. Coronary blood flow was significantly higher in individuals with diagnosed coronary heart disease than in patients without any cardiovascular events. In addition, some studies demonstrated a wide range of threshold values of maximum coronary blood flow velocity (80–150 cm/s) determined by coronary angiography for the diagnosis of significant coronary artery stenoses. In the present prospective study, the threshold value of this index is lower than that in previous diagnostic studies.

To date, ejection fraction remains one of the main echocardiographic parameters used to assess the prognosis of patients with structural cardiac pathology. It is known that the prognostic value of ejection fraction is accurate based on its decrease. However, in the group of asymptomatic patients or those who have not previously suffered a myocardial infarction with normal ejection fraction, the traditional echocardiographic study contains significant limitations in the prognostic assessment. The present study shows statistically more significant prognostic accuracy of coronary blood flow estimation than that of ejection fraction estimation. The authors previously evaluated the prognostic value of high coronary artery velocities and ejection fraction for the prognosis within 3 years [6]. However, in this work, the ejection fraction was not the main prognostic parameter. In contrast to traditional echocardiography, which contains normal values of left ventricular ejection fraction for several limitations in the prognostic informativity of patients with coronary heart disease, coronary artery velocity parameters provide long-term prognostic information suitable for identifying individuals at high risk of adverse cardiovascular events.

## Study limitations

The blood flow in the right coronary artery was not investigated in this work due to limited imaging. The ability to visualize coronary arteries depends on the experience of the performer and the characteristics of the ultrasound machine. The angle between the coronary blood flow and the Doppler beam during velocity measurement may have been incorrect in some cases. In addition, no coronary angiographic information was obtained from the patient cohort of this study. Because this is a single-center study with a short follow-up period, the results should be confirmed in multicenter studies.

# CONCLUSION

The increase in coronary blood flow velocities is a significant and independent predictor of short-term spontaneous adverse events in patients with preserved ejection fraction.

# ADDITIONAL INFORMATION

**Funding.** The study had no external funding.

**Conflict of interest.** The authors declare no conflict of interest.

**Author contributions.** All the authors confirm the compliance of their authorship according to the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication).

The greatest contribution is distributed as follows: *E.S. Kalinina* — the concept and design of the study, the collection and

processing of the materials, the analysis of literary sources, the preparation and writing of the text and editing of the article; *A.V. Zagatina* — the concept and design of the study, collection and processing of the materials, collection and analysis of literary sources, creation of infographics, editing, approval of the final version of the article; *S.A. Sayganov* — the concept of the study, collection and processing of the materials, editing of the article.

**Informed consent for publication.** Not required.

**Ethics approval.** The study protocol No. 5/19 dated 15.05.2019 has been approved by the local ethics committee St. Petersburg University's N.I. Pirogov Clinic of high medical technologies.

**Availability of data and materials.** All data generated or analyzed during this study are included in this published article and its supplementary information files.

## ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

**Источник финансирования.** Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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