Umnov I. N.[1], Bobrov A. L.[2], Alekhin M. N.[3]

[1] Limited liability company «European Institute for Family Health», Saint Petersburg, Russia

[2] Federal state budget military educational institution of higher education «S.M. Kirov Military Medical Academy» Ministry of Defense of the Russian Federation, Saint Petersburg, Russia

[3] Federal state budgetary institution of continuing education «Central Medical Academy» Office of the President of the Russian Federation, Moscow, Russia

Contrast Echocardiography with a Quantitative Assessment of Myocardial Perfusion in Patients with Previous Q-Wave Myocardial Infarction

Objective	To assess possibilities of contrast echocardiography with quantitative evaluation of myocardial perfusion in patients with previous Q-wave myocardial infarction.
Materials and Methods	We examined 15 men (42-72 years) with coronary artery disease and previous myocardial infarction, and pathological Q-wave in 2 or more ECG leads. Quantification of left ventricular (LV) myocardial perfusion was performed by calculating of the ultrasound signal tissue intensity from the LV myocardial segments during intravenous administration of the ultrasound contrast agent (SonoVue). The Tissue intensive curve (TIC) analysis was done in the end-diastolic period before and on the fourth cardiac cycle after applying the «flash». Changes in the intensity of myocardial perfusion (A4, dB) was estimated as the difference between the intensity values of the ultrasound signal in the myocardial segment during the period of filling the contrast bubbles on 4-th cardiac cycle and before applying the «flash». Measurements were performed in 16 segments of the LV. A contrast cardiac magnetic resonance imaging (contrast MRI) was performed in order to verify the LV scar. Fibrotic changes of 50% of myocardial wall or more were considered as signs of post-infarction scar.
Results	The dynamics of perfusion and scar presence in 240 myocardial segments were evaluated. The median A4 was 1 dB (range, -20 to 10 dB). MRI revealed 82 of 240 segments with the large-focal scar. The effectiveness of the diagnostic test (quantitative contrast perfusion echocardiography with A4 assessment) to detect myocardial scar was investigated. ROC curve analysis showed good model quality, AUC=0,787 (0,730-0,837); sensitivity 82.9%; specificity 75.3%; p<0.01. The cut-off point for A4 was -1.
Conclusion	A new approach to quantitative contrast assessment of perfusion allows to identify perfusion disorders with high efficiency in patients with previous Q-wave myocardial infarction.

Keywords	Contrast echocardiography; myocardial perfusion; quantitative analysis; magnetic resonance imaging
For citation	Umnov I. N., Bobrov A. L., Alekhin M. N. Contrast Echocardiography with a Quantitative Assessment of Myocardial Perfusion in Patients with Previous Q-Wave Myocardial Infarction. Kardiologiia. 2020;60(2):17–23. [Russian: Умнов И. Н., Бобров А. Л., Алёхин М. Н. Эхокардиография с контрастным усилением и количественной оценкой перфузии миокарда у больных ишемической болезнью сердца с постинфарктным кардиосклерозом. Кардиология. 2020;60(2):17–23]

Corresponding author	Bobrov Andrey. E-mail: andreybobrov@me.com

Modern methods of contrast-enhanced ultrasound imaging allow the quantitative assessment of myocardial perfusion. The pattern of myocardial blood supply is usually studied using expensive ionizing examination techniques. At present, the possibilities of ultrasound diagnostic methods are only conceptualized [1]. The emergence of intravenous ultrasound contrast enhancement and ultrasound hardware options to assess tissue perfusion has allowed studying myocardial perfusion using ultrasound [2, 3].

Contrast assessment of myocardial perfusion is based on the ultrasound signal intensity from myocardial segments during the saturation, destruction, and subsequent accumulation of the ultrasound intravenous contrast agent within the left ventricular (LV) myocardium. After an intravenous bolus administration of the agent, the heart cavities and coronary blood vessels are filled with the ultrasound contrast agent for 3–5 min. Conventional ultrasound imaging of blood vessels, heart cavities, and viable tissues filled with the contrast agent is followed by the rapid destruction of contrast agent microbubbles.

The intensity of microbubble destruction is determined by the intensity of ultrasound radiation, i.e., the

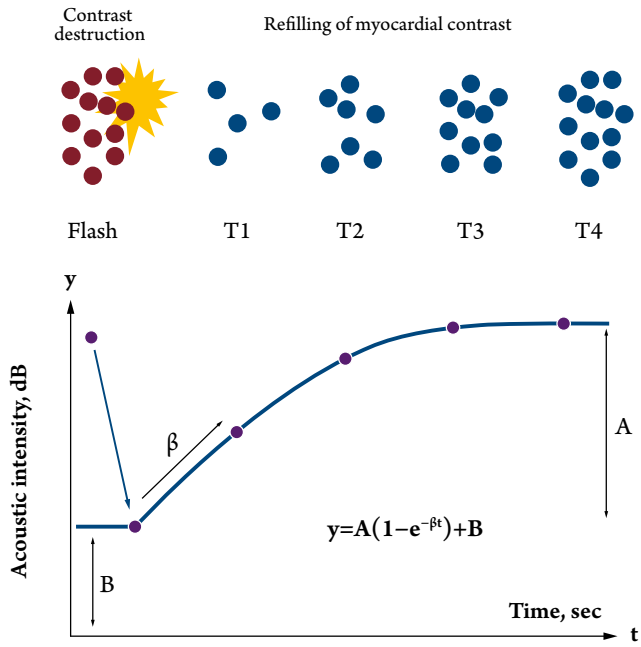
ultrasound mechanical index. Conventional echocardiography uses a mechanical index of 1.0–1.2 units. For optimal scanning of the heart cavities and the assessment of myocardial perfusion using the intravenous contrast agent, the mechanical index is reduced to 0.1–0.2 units. This approach makes it possible to perform ultrasound scanning of the heart for a longer time (3–5 min) without rapid destruction of the contrast agent microbubbles. With conventional mechanical index values of 1.0–1.2 units, the short-term (<1 sec) increase in the intensity of ultrasound radiation, i.e., the flash, destroys microbubbles in the scanning area. This causes a sharp decrease in the intensity of the ultrasound signal from the heart cavities and perfused myocardial segments.

The rate of recovery of the ultrasound signal intensity is determined by the intensity of myocardial coronary perfusion and can be assessed both qualitatively and quantitatively. Myocardial segments with impaired coronary blood supply and poor perfusion are characterized by slow recovery of the ultrasound signal intensity. Healthy segments, by contrast, fully restore their initial characteristics within 3–4 cardiac cycles following the flash [4].

A qualitative approach to the assessment of myocardial perfusion involves a visual assessment of the dynamics of the ultrasound signal intensity from the myocardial wall. Expert assessment allows differentiating segments with reduced contrast during the 5th sec, i.e., during the 4-5th cardiac cycle, following flash from healthy segments. Applying this approach in stress echocardiography increases its sensitivity to detect hemodynamically significant stenoses and preserves its specificity when used in the classical approach for assessment of local contractility. In addition, this approach also enables predicting outcomes of coronary artery disease (CAD) [5–7]. Unfortunately, due to the subjectivity of this technique, its development requires analysis of at least 500 contrast echocardiography examinations [4].

Researchers hoping to increase the objectivity of contrast examinations were encouraged to apply quantitative approaches to assessments of myocardial perfusion [8]. It is believed that the recovery rate of tissue perfusion following flash is determined by an exponential equation (Figure 1), where y during time (t) corresponds to the acoustic signal intensity (dB). Coefficient A is equal to the gain in acoustic intensity, i.e., the segmental contrast intensity (dB), following the application of flash. Coefficient B is equal to the basic acoustic signal intensity (dB) in the segment without contrast measured immediately after flash. Coefficient β is equal to the rate of segmental contrast augmentation (c^{-1}) [4].

Figure 1. Exponential dependence of the acoustic signal intensity from the myocardial segment for four cardiac cycles after the destruction of contrast agent microbubbles



A — the gain of the acoustic signal intensity when the flash is applied in decibels;
B — basic acoustic signal intensity in a segment without contrast;
β — the rate of segmental contrast augmentation, c^{-1}.

Analysis of these coefficients allows quantifying the impairment of the coronary blood supply in the examined myocardial segments. Results demonstrated that this quantitative analysis during stress echocardiography increases sensitivity and specificity of the diagnostic method for detecting hemodynamically significant stenoses [8]. However, the application of contrast-enhanced quantitative perfusion echocardiography requires further study.

The objective of this study was to explore possibilities for the application of contrast echocardiography and quantitative assessment of LV myocardial perfusion in patients with macrofocal, postinfarction cardiosclerosis.

Materials and Methods

This study included 15 male patients with coronary artery disease and macrofocal, postinfarction cardiosclerosis. The patients' age varied from 42 to72 years with median of 60 years. The inclusion criterion was myocardial infarction (MI) and admission to hospital in combination with pathological Q-waves in 2 or more leads on the 12-lead electrocardiogram (ECG) at rest. Patients were excluded from the study if any of the following were present: unstable coronary

ISSN 0022-9040. Kardiologiia. 2020;60(2). DOI: 10.18087/cardio.2020.2.n817

artery disease, exertional angina of all functional classes, cardiomyopathy, heart defects, frequent premature beats (more than ten complexes per minute), atrial fibrillation, complete bundle-branch block, chronic heart failure functional class III–IV, chronic diseases of the respiratory and hematopoietic systems, diabetes, contraindications to magnetic resonance imaging (MRI) and intravenous administration of magnetic and ultrasound contrast agents, failure to image at least 1 of 16 myocardial segments.

During inclusion of patients into the study, the following criteria of pathological Q-waves were recognized on the 12-lead resting ECG: Q-wave ≥30 ms and depth ≥1 mm or a QS complex in leads I, II, aVL, aVF, or V4 V6 in any two leads of a contiguous lead grouping (I- aVL; V1 V6; II–III- aVF); Q-wave in leads V2 V3> 20 ms; or QS complex in leads V2 V3 [9]. The identification of pathological Q-wave in leads V1 V3 corresponded to an anteroseptal view of fibrotic changes in the LV; in V2 V3, an anterior view; in V3 V4, an apical view; in V5 V6, a lateral view; in III, aVF, a posteroinferior view.

All patients underwent contrast resting echocardiography (GE Logiq E9, USA; M5S sensor) with assessment of two-dimensional ejection fraction and index of local LV contractility disturbances following international guidelines [10].

Quantitative assessment of LV myocardial perfusion was made by dynamic evaluation of the ultrasound signal intensity from LV myocardial segments during intravenous bolus infusion of 1 ml of SonoVue. Echolocation was made via apical access in 4-, 2- and 3-chamber views with a focus on the left ventricle. Videos were made after adequate filling of the left chambers of the heart with the ultrasound contrast agent, assessed as the appearance of homogeneous echo-positive staining of the entire ventricular cavity. We excluded videos with sections of large coronary vessels passing through the myocardium. After analyzing the recorded videos, assessment of local LV myocardial contractile function was based on the consolidated opinion of two physicians specializing in echocardiography.

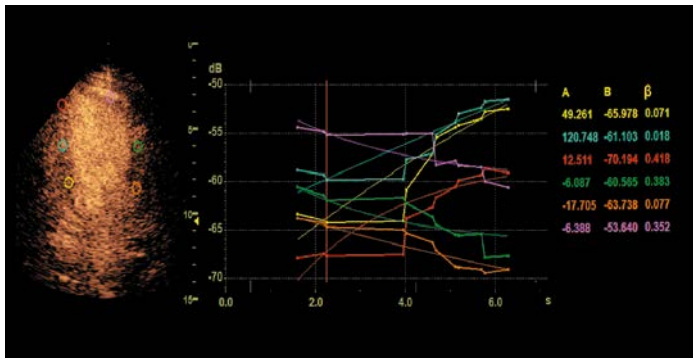
Myocardial perfusion was evaluated after applying a series of high-energy ultrasound pulses, i.e., flashes, 20 within 1 sec, that destroy the contrast agent microbubbles, followed by visualization of the myocardium and assessment of the bubble refilling in the end-diastolic period of the cardiac cycle. The quantitative assessment of the ultrasound signal intensity from the myocardial segments was made before the application of a flash and during the 4th cardiac cycle after the application of the flash using special time intensity curve (TIC) analysis software. In each assessed end-diastolic period, two adjacent frames closest to the top of the ECG R-wave were highlighted. Measurements were made in these highlighted frames.

Local contractility and myocardial perfusion were assessed in 16 segments of LV: Four apical, six middle, and six basal segments during a sequential scanning in the three indicated apical sections. Changes in the disturbances of local contractility were graded using a semiquantitative method that identified segments with normal contractility, hypokinesia, akinesia, or dyskinesia. A quantitative assessment of myocardial perfusion was performed in each of the 16 LV segments using hardware TIC analysis with echocardiographic scanner option. After the examination, the recorded videos of contrast echocardiography were analyzed in three apical positions. With the use of a circular sector of at least 50% myocardial wall thickness, a central portion of each LV segment was highlighted. The calculation was made at the time point corresponding to the top of the ECG R-wave or the end of ventricular diastole.

For each segment in the examined sections, the software automatically analyzed dynamically the ultrasound signal intensity from the myocardium and built dot plots of the ultrasound intensity before and following the application of the flash. The exponential equation of the time-dependence of an assessed parameter was additionally calculated, i.e., the time curve of the ultrasound signal intensity before and for four cardiac cycles following application of the flash. Calculation of the exponential function took into account the absolute values of the acoustic intensity of a myocardial segment in 5 end-diastolic intervals (two measurements of each) corresponding to the ECG R-wave just before and in the 1st, 2nd, 3rd, and 4th cardiac cycles after the application of the flash. Coefficients of the equations obtained for each analyzed segment are provided in a scan table (Figure 2).

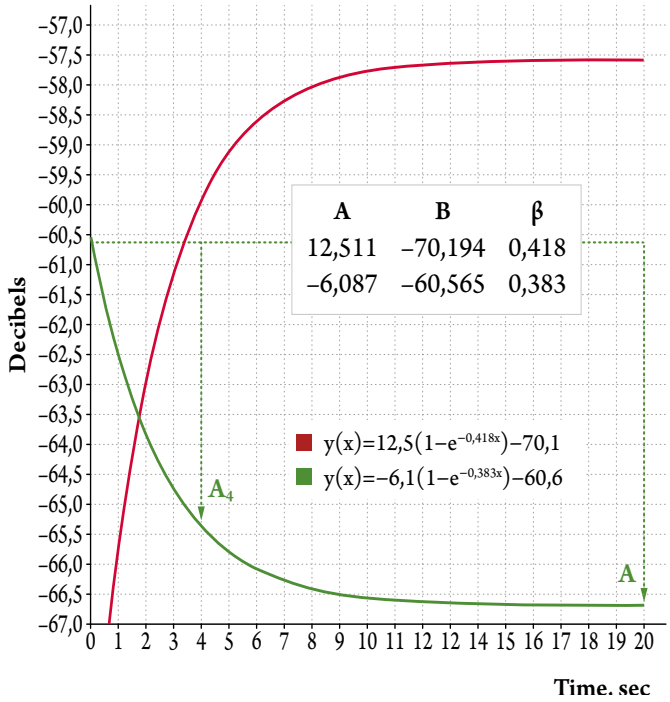
Values of the following automatically calculated parameters, i.e., the coefficients of the exponential equation, are taken into account for each of the 16 myocardial segments, A, B, and β. The parameter Aβ (myocardial blood flow index) was calculated as the product of the two indicators A and β, thus determining to the greatest extent, the disturbances of myocardial perfusion. The parameter A4 was additionally taken into account. It was defined as the difference between the instantaneous value of the ultrasound signal intensity in the myocardial segment being examined during the filling of contrast agent bubbles during the 4th cardiac cycle, i.e., the last of two measurements, and the value before the application of the flash. It was assumed that positive values of A and A4 confirm normal perfusion and

Figure 2. Example contrast echocardiography of 59 year old patient G. with postinfarction, fibrotic changes in the LV lateral wall



On the left, is a two-dimensional echocardiogram in the apical four-chamber view. Red, blue, and yellow circles are located in the interventricular septum, and green, orange, and purple circles are in the LV lateral wall. In the center is shown the exponential dependence of the acoustic signal intensity from the myocardial segment before and for four cardiac cycles after the destruction of contrast agent microbubbles by flash. Thin curves with the same color represent the simulation of the exponential function of the acoustic signal intensity from the myocardial segments over time. The red vertical line represents the beginning of the data analysis for plotting an exponential curve. It corresponds to the end-diastolic period before application of the flash. Healthy segments of the interventricular septum demonstrate the positive dynamics of the acoustic signal intensity. Segments of the LV lateral wall with fibrotic changes show the negative dynamics of the assessed parameter. On the right are listed the coefficients of the exponential equations for each of the examined segments.

Figure 3. Example of computer simulation of the exponential function of the acoustic signal intensity from the myocardial segments over time in 59 year old patient G. based on the data of five intervals before and within 4 sec after the flash



The curves of the variable assessed over time in the interventricular septum (red) and in LV lateral wall (green) are plotted based on the calculated coefficients in the above table. Parameters A4 and A for the left ventricular lateral wall are provided on the graph.

that negative values indicate disturbances of myocardial perfusion in the examined segment (Figure 3).

All subjects underwent cardiac MRI (1.5 Tesla) enhanced with gadolinium chelates to verify macrofocal LV myocardial fibrosis. The presence or absence of signs of fibrosis of 50% or more of the diastolic thickness of each of the 16 LV myocardial segments was determined.

Data were statistically analyzed with MedCalc 19.0.7 software (Belgium). Data are presented as medians and interquartile ranges [25th percentile; 75th percentile]. Receiver operating characteristic (ROC) curve analysis of the effectiveness of the diagnostic model was performed, and the area under the curve (AUC) and the 95% confidence interval (CI) were calculated. Differences were considered significant at $p<0.05$.

Results

Pathological ECG Q-waves were analyzed for all patients included in the study. The median sum of the leads with signs of pathological Q-waves was 3 (2-5) leads. The ECG detected 1 affected LV region in 1 patient; 2 LV regions in 12 patients; 3 LV regions in 2 patients; posteroinferior LV segments in 4 patients; and anteroseptal, anterior, apical, and lateral LV segments in 11 patients. The median LV ejection fraction was 49 [28; 58] %. Disturbances of local contractility were registered in all examined patients. The median disturbance index was 1.6 [1.1; 2.5] units. The most frequent contractility disturbances were registered in apical (n=14), anterior (n=10), and anteroseptal (n=6) LV regions. Less frequent disturbances were identified in septal (n=4), lateral (n=4), posterior (n=3), and inferior (n=2) LV regions.

Contrast-enhanced MRI identified 82 (34.2%) myocardial segments with the signs of macrofocal fibrotic lesions. The dynamics of perfusion and fibrotic changes were evaluated in a total of 240 myocardial segments. During perfusion echocardiography, median A4 was 1 dB (-20–10 dB). The following results were obtained for the calculated parameters: A=0.9 dB (from –18.6 to 12.0 dB); B=–66.0 dB (from –76.0 to 62.0 dB); β=0.70 c^{-1} (from 0.06 to 4.10 c^{-1}); Aβ=0.72 dB / c^{-1} (from –7.44 to 49.20 dB / c^{-1}).

The efficacy of the diagnostic test, i.e., contrast-enhanced quantitative perfusion echocardiography, for the detection of fibrotic changes in the myocardium was assessed. The initial examination was made to assess A4. The ROC-curve analysis showed good quality of the model (Figure 4): AUC=0.787 ($p<0.01$), model

ISSN 0022-9040. Kardiologiia. 2020;60(2). DOI: 10.18087/cardio.2020.2.n817

Table 1. Efficacy of contrast-enhanced quantitative perfusion echocardiography in the identification of myocardial fibrotic changes (p <0.01)

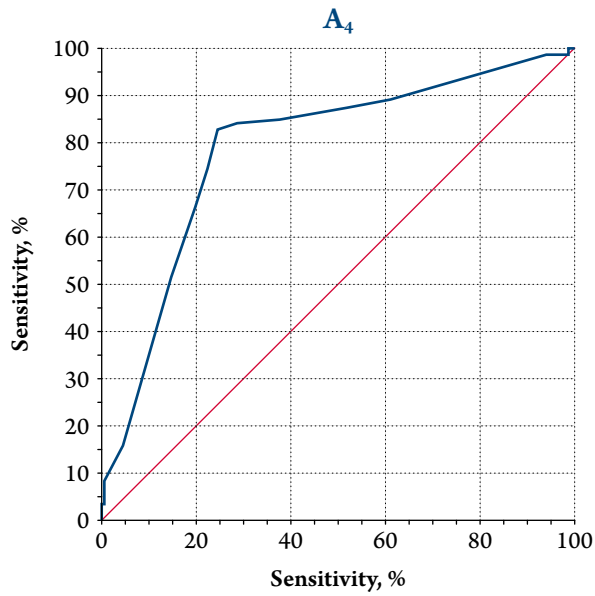
Показатель	A_4	A	B	β	Aβ
AUC	0.787	0.814	0.639	0.821	0.787
95% CI AUC	0.730–0.837	0.759–0.861	0.575–0.700	0.767–0.867	0.730–0.837
Sensitivity. %	82.9	84.1	84.1	85.4	82.9
Specificity. %	75.3	76.6	41.1	71.5	75.3
Cut-off point	-1 dB	-1.1 dB	-69 dB	0.6 c^{-1}	-0.35 dB/c^{-1}
100% sensitivity of the model at	> 8 dB	> 8.2 dB	< -76 dB	> 3.1 c^{-1}	> 21.6 dB/c^{-1}
100% specificity of the model at	< -8 dB	< -8.5 dB	> -52 dB	< 0.1 c^{-1}	<-3.72 dB/c^{-1}

sensitivity=82.9%, and specificity=75.3%. The predictive value was 34.2% for the positive result and 65.8% for the negative result. The cut-off point for A4 at the indicated sensitivity and specificity of the model was equal to –1 dB.

Parameters A and β showed the best results. In both cases, the model quality was evaluated as very good. AUC values were 0.814 and 0.821 (p <0.01), with sensitivities of 84.1% and 85.4%, and specificities of 76.6% and 71.5%, respectively (Figure 5). The cut-off point for A was –1.1 dB, which was almost the same as the corresponding values for A4.

The remaining calculated parameters were somewhat worse. In the case of Aβ and B, the model quality was assessed as very good and medium. AUC values were 0.787 and 0.639 (p<0.01) with sensitivities of 82.9% and 84.1%, and specificities of 75.3% and 41.1%, respectively. The remaining statistical indicators of the efficacy of the calculated parameters for detection of fibrotic changes in the myocardium are shown in Table 1.

Figure 4. Assessment of the efficacy of the contrast-enhanced quantitative perfusion echocardiography diagnostic test for the detection of fibrotic changes in the myocardium by calculation of A_4. Data sheet and ROC-curve



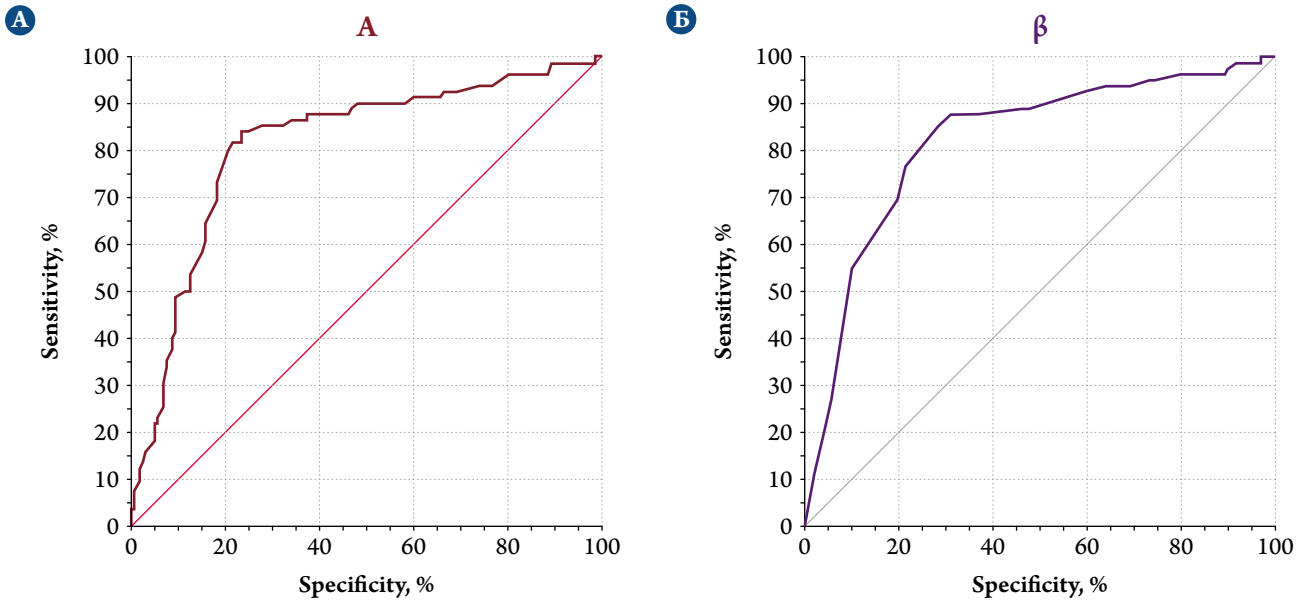
Discussion

The current data confirm that contrast-enhanced quantitative perfusion echocardiography can be used for diagnosis of myocardial malperfusion [8]. We tested a diagnostic model that included the use of the most reliable in vivo diagnostic method for macrofocal, postinfarction cardiosclerosis: contrast-enhanced, cardiac MRI. We hypothesized that there was not adequate coronary circulation in the myocardial segments with signs of delayed accumulation of gadolinium, which was anamnestically associated with prior Q-wave myocardial infarction. We are the first to suggest that myocardial malperfusion could be verified by analyzing the dynamics of several parameters that describe the exponential dependence of the acoustic signal intensity from the myocardial segments during four cardiac cycles following application of the flash.

Additional testing was performed of a more straightforward approach to the analysis of perfusion and the quantitative assessment of the acoustic signal intensity from the myocardial segments at only two moments: 1) before the application of flash and 2) in the 4th cardiac cycle after the application of the flash. This method did not require registration of the acoustic signal intensity at five intervals, i.e., before and for 4 cardiac cycles after the application of the flash, followed by the simulation of the exponential function. Thus, this method could be considered more straightforward.

Some researchers have suggested plotting an exponential function curve for the acoustic signal intensity based on the evaluated dynamics of the parameter for ten cardiac cycles following the application of flash [11]. We believe this approach is not justified. While observing the myocardial segments with signs of decreased perfusion, we detected inverted dynamics of the acoustic signal intensity after flash. We found that saturation of myocardial microvessels with the contrast agent bubbles after the application of flash decreases progressively for 4–6 cardiac cycles. This is likely due to

Figure 5. Figure 5. Assessment of the efficacy of contrast-enhanced quantitative perfusion echocardiography with the calculation of A (A) и β (B)) for the detection of fibrotic changes in the myocardium. Datasheet and ROC-curves



delayed washout of blood plasma containing the inert gas from destroyed microbubbles of the ultrasound contrast agent in the presence of impaired blood supply. Subsequently, the concentration of undestroyed bubbles begins to increase. Thus, the acoustic signal intensity of the myocardial segments first decreases and then begins to recover after 4–6 cardiac cycles. In the segments with normal perfusion, on the contrary, the microbubble concentration begins to increase following flash, which is manifested by the recovery of the acoustic signal intensity from the myocardium within 3–4 cardiac cycles. The approach involving quantitative analysis of the acoustic signal intensity with data averaging for ten cardiac cycles following the application of flash reduces this two-phase dynamics.

Another important distinction of the proposed approach for quantitative assessment of the perfusion disturbances was the calculation of the acoustic signal intensity from myocardial segments at the end-diastolic rather that at the end-systolic period of the cardiac cycle. The authors who suggested the use of the end-systolic interval believed that during this period the myocardium has maximal thickness and the intramyocardial vessel have minimal diameters [12]. According to them, this approach simplifies the positioning of the control sector to measure the acoustic signal intensity and reduces the possibility of getting signal into a vessel section. Our approach significantly simplifies the search for the required period as it corresponds to the top of the ECG R-wave. The myocardial microcapillaries are filled with blood to a greater degree in the diastolic period. The method also involved insuring absence of major coronary vessels in the scanned myocardial sections. Thus, a higher blood filling and contrast staining of the myocardial wall can be expected in the diastolic period.

As expected, analysis of the proposed diagnostic approach demonstrated that parameters A and β are the most effective exponential coefficients for the diagnosis of malperfusion. Parameters A and β characterized, respectively, the degree of increase/decrease and the degree of slope, i.e., the rate of increase/decrease of the acoustic signal intensity from the myocardium. The efficacy of using these coefficients was very good, with 85–86% sensitivity and 75–77% specificity.

This simplified approach for calculating the absolute increase/decrease in the acoustic signal intensity (A4) following the application of flash in the 4th cardiac cycle demonstrated the high efficacy of the model for diagnosing malperfusion. Negative values of A4, reflecting decreased intensity of the acoustic signal following the application of flash, were indicative of circulatory disturbances in the examined myocardial segment with 83% sensitivity and 75% specificity. This simplified approach saves time and can be used if no software is available for calculating the exponential function. At the same time, this approach to the diagnosis of myocardial malperfusion was only insignificantly less effective.

Conclusions

A new approach to the quantitative assessment of myocardial perfusion using contrast echocardiography allows high-efficacy detection of myocardial malperfusion associated with fibrotic changes due to postinfarction cardiosclerosis. The registration of the full dynamics of the acoustic signal intensity from myo-

ISSN 0022-9040. Kardiologiia. 2020;60(2). DOI: 10.18087/cardio.2020.2.n817

cardial segments before and during four cardiac cycles after the application of flash allows good-quality identification of myocardial malperfusion associated with fibrotic lesions. Application of this technique in the future is likely to permit 1) differential diagnosis between hibernating myocardium and focal fibrotic lesions, 2) high-sensitivity and specificity diagnosis of transient myocardial ischemia, 3) improvement of the accuracy of ultrasound diagnosis of coronary artery disease, 4) reduction of radiation exposure, since there is no need for coronary angiography and multislice computed tomography angiography, and 6) reduction of the examination cost.

The authors express their gratitude to Rud Sergei Dmitrievich, Candidate of Medical Sciences, Associate Professor at the Department of Radiology of SM Kirov Military Medical Academy, and Dubitskiy Dmitriy Leonidovich, Candidate of Medical Sciences, radiologist at the Department of Radiology of Children's Research Center for Infectious Diseases, Federal Medical and Biological Agency, for their invaluable contribution to the performance and analysis of the results of magnetic resonance imaging of the heart.

No conflict of interest is reported.

The article was received on 21 / 09 / 19

REFERENCES

1. Ansheles A.A., Sergienko V.B. Myocardial Perfusion Imaging Modalities: What do we Really see? Kardiologiia. 2017;57(7):5–12. [Russian: Аншелес А.А., Сергиенко В.Б. Перфузия миокарда: что понимается под этим термином при визуализации различными методами лучевой диагностики? Кардиология. 2017;57(7):5-12]. DOI: 10.18087/cardio.2017.7.10000
2. Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of Myocardial Blood Flow With Ultrasound-Induced Destruction of Microbubbles Administered as a Constant Venous Infusion. Circulation. 1998;97(5):473–83. DOI: 10.1161/01.CIR.97.5.473
3. Karmazanovsky G.G., Stepanova Yu.A., Askerova N.N. History of Development of Contrast-Enhanced Imaging at Ultrasound. Medical Visualization. 2015;2:110–9. [Russian: Кармазановский Г.Г., Степанова Ю.А., Аскерова Н.Н. История развития контрастного усиления при ультразвуковом исследовании. Медицинская визуализация. 2015;2:110-9]
4. Porter TR, Mulvagh SL, Abdelmoneim SS, Becher H, Belcik JT, Bierig M et al. Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update. Journal of the American Society of Echocardiography. 2018;31(3):241–74. DOI: 10.1016/j.echo.2017.11.013
5. Gaibazzi N, Rigo F, Squeri A, Ugo F, Reverberi C. Incremental value of contrast myocardial perfusion to detect intermediate versus severe coronary artery stenosis during stress-echocardiography. Cardiovascular Ultrasound. 2010;8(1):16. DOI: 10.1186/1476-7120-8-16
6. Gaibazzi N, Reverberi C, Lorenzoni V, Molinaro S, Porter TR. Prognostic Value of High-Dose Dipyridamole Stress Myocardial Contrast Perfusion Echocardiography. Circulation. 2012;126(10):1217–24. DOI: 10.1161/CIRCULATIONAHA.112.110031
7. Kutty S, Bisselou Moukagna KS, Craft M, Shostrom V, Xie F, Porter TR. Clinical Outcome of Patients With Inducible Capillary Blood Flow Abnormalities During Demand Stress in the Presence or Absence of Angiographic Coronary Disease. Circulation: Cardiovascular Imaging. 2018;11(10):e007483. DOI: 10.1161/CIRCIMAGING.117.007483
8. Abdelmoneim SS, Dhoble A, Bernier M, Erwin PJ, Korosoglou G, Senior R et al. Quantitative myocardial contrast echocardiography during pharmacological stress for diagnosis of coronary artery disease: a systematic review and meta-analysis of diagnostic accuracy studies. European Heart Journal - Cardiovascular Imaging. 2009;10(7):813–25. DOI: 10.1093/ejechocard/jep084
9. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA et al. Fourth universal definition of myocardial infarction (2018). European Heart Journal. 2019;40(3):237–69. DOI: 10.1093/eurheartj/ehy462
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal – Cardiovascular Imaging. 2015;16(3):233–71. DOI: 10.1093/ehjci/jev014
11. Leong-Poi H, Le E, Rim S-J, Sakuma T, Kaul S, Wei K. Quantification of myocardial perfusion and determination of coronary stenosis severity during hyperemia using real-time myocardial contrast echocardiography. Journal of the American Society of Echocardiography. 2001;14(12):1173–82. DOI: 10.1067/mje.2001.115982
12. Eskandari M, Monaghan M. Contrast echocardiography in daily clinical practice. Herz. 2017;42(3):271–8. DOI: 10.1007/s00059-017-4533-x