DIAGNOSTIC CAPABILITIES OF MAGNETIC RESONANCE IMAGING IN ASSESSING THE MYOCARDIAL PERFUSION IN CASES OF ISCHEMIC DISORDERS

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ABSTRACT

Magnetic resonance imaging (MRI) of the heart has proven itself as an important tool for the evaluation of myocardial perfusion and for the diagnostics of myocardial ischemia. Due to its high spatial resolution and absence of X-ray radiation, MRI of the heart allows for precise diagnosing subendocardial ischemia without any adverse effects, which makes it a valuable method for detecting the ischemic heart disease. Recent advances in cardiac MRI and in post-processing have allowed for moving from qualitative to quantitative evaluation of the stress perfusion cardiac MRI, which has significantly increased the objectiveness and the precision of diagnostics. Quantitative evaluation of myocardial perfusion using the MRI provides a possibility of objective evaluation of myocardial ischemia, which can contribute to improved detection of coronary microvascular dysfunctions. The integration of quantitative perfusion MRI with other methods, such as the kinematic MRI, the delayed increase of gadolinium levels and the T1/T2-mapping, allows for deeper understanding the pathophysiology and improving the prediction of outcomes for various cardio-vascular diseases. The review addresses modern research works on cardiac MRI with regard to diagnostics and predicting of ischemic heart disease, coronary microvascular dysfunctions or non-ischemic cardiomyopathy, focusing on the quantitative approach in the evaluation of myocardial perfusion and its potential use in clinical practice.

Keywords: *magnetic resonance imaging; MRI of the heart; myocardial perfusion; coronary artery disease; CMD; coronary artery disease; CAD; prediction of cardiovascular diseases.*

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INTRODUCTION

Stress perfusion magnetic resonance imaging (MRI) of the heart has become an important method for the diagnostics of myocardial ischemia due to its high spatial resolution and the ability to detect subendocardial ischemia, making it preferable comparing to the radio-isotopic methods, such as single-photon emission computed tomography (SPECT) and positron-emission tomography (PET), especially taking into consideration the absence of radiation exposure [1, 2]. Moreover, MRI of the heart allows for performing a combined evaluation of the cardiac activity within a single examination, including the analysis of the contractile functions of the myocardium (using kinematography), the detection of myocardial fibrosis and scars by means of using the method of late increase of the gadolinium levels (late gadolinium enhancement, LGE), as well as the characterization of myocardial tissues using the parametric mapping. These methods complement the routine stress cardiac MRI that is used for the evaluation of myocardial perfusion, providing a more detailed understanding of the structure and functions of the cardiac muscle [1].

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ДИАГНОСТИЧЕСКИЕ ВОЗМОЖНОСТИ МАГНИТНО-РЕЗОНАНСНОЙ ТОМОГРАФИИ В ИССЛЕДОВАНИИ МИОКАРДИАЛЬНОЙ ПЕРФУЗИИ ПРИ ИШЕМИЧЕСКИХ СОСТОЯНИЯХ

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АННОТАЦИЯ

Магнитно-резонансная томография (МРТ) сердца зарекомендовала себя как важный инструмент для оценки миокардиальной перфузии и диагностики ишемии миокарда. Благодаря высокому пространственному разрешению и отсутствию рентгеновского излучения МРТ сердца позволяет точно диагностировать субэндокардиальную ишемию без каких-либо побочных эффектов, что делает её ценным методом для выявления ишемической болезни сердца. Недавние достижения в области МРТ сердца и постпроцессинговой обработки позволили перейти от качественной к количественной оценке стресс-перфузионной МРТ сердца, что значительно повысило объективность и точность диагностики. Количественная оценка миокардиальной перфузии с помощью МРТ предоставляет возможность объективно оценить степень ишемии миокарда, что может способствовать улучшенному выявлению коронарной микрососудистой дисфункции. Интеграция количественной перфузионной МРТ с другими методами, такими как кинематическая МРТ, позднее повышение уровня гадолиния и T1/T2-картирование, позволяет глубже понять патофизиологию и улучшить прогнозирование исходов различных сердечно-сосудистых заболеваний. В обзоре рассматриваются современные исследования МРТ сердца в диагностике и прогнозировании ишемической болезни сердца, коронарной микрососудистой дисфункции и неишемической кардиомиопатии с фокусом на количественный подход в оценке миокардиальной перфузии и её потенциальное применение в клинической практике.

Ключевые слова: *магнитно-резонансная томография; МРТ сердца; миокардиальная перфузия; ишемическая болезнь сердца; ИБС; коронарная микрососудистая дисфункция; КМД; прогнозирование сердечно-сосудистых заболеваний.*

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Modern advances in the field of scanning sequences and data processing allow for performing the quantitative analysis of myocardial perfusion, which promotes to the transition from qualitative to quantitative assessment of stress perfusion, providing a more objective diagnostics of ischemic changes. Quantitative methods may turn out to be useful for detecting coronary microvascular dysfunctions (CMD) and for studying the pathogenesis of non-ischemic cardiomyopathy. As a result, the area of application for the stress perfusion MRI of the heart becomes significantly expanded.

The research work also contains an analysis of current literature data concerning the diagnostics and prediction of ischemic heart disease (IHD), CMD and non-ischemic cardiac disease with an accent to the role of perfusion cardiac MRI.

List of abbreviations

HCM — hypertrophic cardiomyopathy
DCM— dilated cardiomyopathy
IHD — ischemic heart disease
CMD — coronary microvascular dysfunction
MRI — magnetic resonance imaging (tomography)
SPECT — single-photon emission computed tomography
PET — positron-emission tomography
HFpEF — heart failure with preserved ejection fraction
AUC — area under the curve
CFR — coronary flow reserve
ECV — extracellular volume
FFR — fractional flow reserve
GLS — global longitudinal strain
LGE — late gadolinium enhancement
MACE — major adverse cardiovascular events
MBF — myocardial blood flow
MPR — myocardial perfusion reserve
MPRI — myocardial perfusion reserve index

Methodology of searching the research works

The search of the trials was undertaken in the following data bases: eLibrary, PubMed/MEDLINE and Google Scholar until December 2024, using the following key words: «myocardial ischemia», «cardiovascular magnetic resonance», «coronary artery disease», «microvascular dysfunction», «heart failure». As a result of the search, a total of 4803 articles were found in the PubMed/MEDLINE data base, 3982 — in Google Scholar and 1989 — in the eLibrary.

As the first stage, the authors have excluded the duplicates, while the screening phase with an assessment of abstracts and titles of the detected research works was aimed to evaluate the conformity to the topic of the present review. The next phase included an evaluation in accordance with the following inclusion criteria: the research published in Russian or in English; the research is published in a peer-reviewed scientific journal; the research was undertaken using humans or animals; the research being a literature review or an original article containing the abovementioned key words; the research describes the application of cardiac MRI in the diagnostics of IHD severity degree, in characterizing the functional impairment of coronary microvessels and in the assessment of the prognostic significance of these parameters in patients with various cardio-vascular diseases, including IHD, hypertrophic and dilated cardiomyopathy, as well as heart failure with preserved ejection fraction. Ultimately, 71 trials were included into the review.

DIAGNOSTIC SIGNIFICANCE OF MAGNETIC RESONANCE IMAGING OF THE EPICARDIAL CORONARY ARTERIES

Increased spatial resolution of MRI allows for detecting the subendocardial ischemia by means of qualitative visual evaluation, which provides higher diagnostic precision comparing to SPECT in the diagnostics of IHD [1].

More than 10 years ago, the CE-MARC large single-center prospective randomized research has demonstrated that the stress MRI is superior comparing to the SPECT in terms of the efficiency (area under the curve [AUC] — 0.89 vs. 0.74, respectively, p <0.0001) in detecting the clinically significant IHD, which was defined as ≥70% narrowing of the vessel lumen according to data from invasive coronary angiography [3]. Further analysis of the CE-MARC trial performed by P.P. Swoboda et al. [4], included a comparison of the diagnostic precision of the stress-LGE and stress-rest methods for detecting the ischemia. When using the stress-LGE method, ischemia was detected as the perfusion defect with no signs of infarction according to data from delayed LGE-visualization, while the stress-rest method detects ischemia by the presence of perfusion defect solely upon the stress-visualization. It was found that the stress-LGE method demonstrates higher diagnostic precision with a sensitivity of 75.6% and with the specificity of 93.1% comparing to the stress-rest method, which had a sensitivity of 73.6% along with a specificity of 93.1%.

The evaluation of the spreading degree of myocardial infarction with the aid of LGE represents an important benefit of cardiac MRI, increasing the diagnostic precision in detecting the obstructive IHD. In a recent Phase III clinical trial, A.E. Arai et al. [5] have evaluated the diagnostic precision of stress perfusion MRI of the heart comparing to SPECT in terms of detecting the significant IHD, defined as more than 70% stenosis in the results of coronary angiography. The authors have revealed that stress-MRI of the heart has better diagnostic characteristics with an AUC of 0.88 comparing to the AUC 0.74 for SPECT (p <0.001)

The PACIFIC-2 research was a prospective comparative trial aimed at the evaluation of the

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diagnostic efficiency of qualitative stress perfusion MRI of the heart, of the qualitative 99mTc-SPECT and of the quantitative 15O-H2O PET in detecting the hemodynamically significant IHD using the parameter of fractional flow reserve (FFR) <0.8 as a standard criterion. In this research, the quantitative PET was superior comparing to the qualitative perfusion MRI of the heart and comparing to the SPECT in terms of the AUC values and precision (0.76, 0.66 and 0.66; 70%, 70% and 67%, respectively), however, there were no significant differences detected in the total diagnostic precision between these three methods. It is important to note that, within the framework of this protocol, PET had a benefit of quantitative analysis, while the heart MRI and SPECT were evaluated qualitatively [6].

Each of the methods mentioned above has its specific features, benefits and limitations. MRI of the heart and SPECT in the diagnostics of myocardial ischemia are based predominantly on the visual evaluation, while PET more often relies on the quantitative evaluation of the myocardial circulation. This is due to the fact that PET is capable of providing precise and reproducible measurements of the circulation in the myocardium, both in the stress state and at rest – due to practically linear relation between the indicator uptake and its concentration. The comparative trials on the visualization of myocardial perfusion constantly demonstrate high diagnostic precision for PET. Nevertheless, despite these benefits, PET also has significant drawbacks, including high cost and short half-life of the used radionuclides. The latter requires either the presence of nearly located cyclotron or the use of special radioactive markers with longer half-lives, such as flurpiridaz (18F) [7], which may limit the accessibility of PET.

Despite the advance in modern visualization technologies, SPECT remains the most widely used method for evaluating the myocardial ischemia, mainly due to its high accessibility. One of the key benefits of SPECT is the possibility of conducting the examination in the settings of physical loading, which is especially important for patients with contraindication to pharmacological stress-tests [8]. However, this method is characterized by relatively low spatial resolution, which limits its diagnostic precision comparing to such methods as PET and MRI of the heart [9]. Another important problem is the radiation load, making this method potentially unsafe for some categories of patients.

Cardiac MRI, on the contrary, has a significant benefit due to the fact that it is not associated with radiation exposure, providing high spatial resolution and detailed information on the impairment of the myocardium by means of using the LGE method as a part of combined examination protocols. Nevertheless, there are certain limitations related to the presence of metallic implants and to the necessity of using contrasting agents, which can be problematic for patients with chronic kidney diseases or implanted medical devices. New developments, such as ferumoxytol — based contrasting agents for patients with chronic renal failure [10] and the methods of broadband visualization for patients with metallic implants [11], can aid in overcoming these limitations.

SPECT represents a modern approach to the visualization of myocardial perfusion, allowing for performing a complete quantitative evaluation of myocardial blood flow (MBF) by means of dynamic scanning [12]. Just like the stress perfusion MRI of the heart, SPECT combines the possibilities of evaluating the perfusion with the evaluation of the morphology in the coronary arteries, similar to the one provided by the coronary angiography [13]. However, despite these benefits, SPECT has a number of limitations related to the necessity of using iodine-containing contrasting agents and to the exposure of ionizing radiation, which constitutes a specific problem for patients with severe chronic kidney diseases or for the young men.

Thus, each of the mentioned visualization methods has its benefits and limitations, which has to be taken into account when choosing the optimal approach for a specific patient.

PROGNOSTIC SIGNIFICANCE OF MAGNETIC RESONANCE IMAGING OF THE HEART IN TERMS OF DETECTING THE IMPAIRMENT OF CORONARY ARTERIES

The quantitative methods of cardiac perfusion MRI have significantly progressed over the recent years and they are still being actively researched. The diagnostic precision of cardiac stress perfusion MRI was evaluated by A.D. Villa et al. [14] with the involved physicians having various levels of training and experience. The results have demonstrated that the third level certified specialists from the European Society of Cardiology (ESC) / the European Association of Cardiovascular Imaging (EACVI) were able to detect clinically significant IHD in 83.6% of the cases, while the second level examiners have achieved a precision of 65.7%, with the first level showing only 55.7% (p <0.001). In this research, the automatic quantitative analysis has demonstrated the results comparable to those obtained by the third qualification level physicians (86.3% of the cases; p=0.56).

In another auxiliary research (CE-MARC), it was shown that the stress-MBF and the myocardial perfusion reserve (MPR), when measured using the quantitative stress perfusion MRI of the heart, were reaching the AUC of 0.89 (95% CI: 0.83–0.96) and 0.87, respectively, for detecting the clinically significant IHD (stenosis exceeding 70%). The AUC values obtained upon the visual evaluation by an expert, were 0.88 (95% CI: 0.81–0.95). The differences in diagnostic precision between quantitative and visual evaluation were not statistically significant (p=0.72). Besides, the addition of MBF values at rest for calculating the myocardial perfusion reserve (MPR) did not result in a significant increase in AUC (p=0.79) [15].

The recent research by R. Crawley et al. [16] has evaluated the diagnostic precision of automated high-resolution perfusion mapping in detecting the clinically significant IHD. The investigators have found that, with the MBF of ≤1.94 ml/g per minute and the MPR of ≤1.97, one can effectively identify the clinically significant IHD (FFR ≤0.80) when examining the coronary arteries (AUC 0.85 and 0.96, respectively, p <0.001 for both parameters). Thus, the quantitative stress perfusion MRI of the heart can provide an objective and precise evaluation of myocardial ischemia.

The qualitative evaluations of stress perfusion MRI can underestimate the ischemic load in patients with multivascular IHD [17, 18]. T. Kotecha et al. [19] have analyzed the diagnostic efficiency of quantitative perfusion mapping comparing to visual evaluation of cardiac perfusion MRI in detecting multivascular lesions in the coronary arteries. The authors have found that the ischemic load, detected using the quantitative mapping, was significantly higher in cases of multivascular lesions comparing to the ischemic load evaluated visually (in cases of tri-vascular involvement — 100% versus 56%, in cases of the bivascular one — 63% versus 41%; p <0.001), however, significant differences were not shown for single-vessel impairment (25% versus 25%). Hence, the quantitative mapping of perfusion more precisely defines the degree of impairment in the coronary arteries comparing to the visual evaluation methods. This is an additional important benefit of quantitative approaches in evaluating the perfusion by means of cardiac MRI in the diagnostics of the impairment in epicardial coronary arteries.

Cardiac MRI plays an important role in assessing the severity of IHD, allowing for precise determination of the ischemic changes and the zones of myocardial infarction. This makes the method an indispensable tool for risk stratification in IHD patients. In a large multicenter retrospective research named SPINS [20], which has investigated the prognostic significance of cardiac stress-MRI in patients with stable angina, a total of 2349 patients were enlisted from 13 medical institutions in USA. The mean follow-up time was 5.4 years. The patients, which had no signs of ischemia or LGE, have shown low rates of fatal outcomes (all-cause) and low rates of nonfatal myocardial infarction (<1%) with the need for coronary re-vascularization (from 1% to 3%). In contrast, patients with signs of both ischemia and LGE had a more than four-fold increase in the all-cause mortality rates or in the rates of nonfatal myocardial infarction, along with a ten-fold increase in the need of coronary re-vascularization.

Recently, an evaluation of the efficiency of cardiac stress-MRI was carried out for the purpose of risk stratification in more specific population groups. T. Pezel et al. [21] have assessed the long-term prognostic factors of cardiac stress perfusion MRI among 2,295 patients with cardio-vascular risk factors, but without the confirmed IHD. During a mean follow-up period of 8.3 years, major adverse cardiovascular events (MACE) were reported in 203 participants. Ischemia and previously undetected myocardial infarction, revealed by using the MRI of the heart, became a potent predictor of developing MACE and fatal outcomes caused by cardiac failure. T. Pezel et al. [22] have also investigated the long-term prognosis of coronary re-vascularization, conducted based on the cardiac MRI findings, i.e. any re-vascularization performed within 90 days after the MRI. The research included 31,762 patients with suspected IHD, the mean follow-up time for which was 6.0 years. The trial has shown that stress- induced ischemia and LGE were the independent predictors of all-cause mortality. Besides, re-vascularization based on the cardiac MRI findings, was associated with lower mortality rates among the patients with ischemia in ≥6 segments (severe degree), but it did not show any benefits in patients with the ischemia of <6 segments (mild or moderate degree) [22].

M. Kinnel et al. [23] have investigated the prognostic value of cardiac stress perfusion MRI in patients with known diseases of the coronary arteries with a mean follow-up time of 4.2 years. The induced ischemia was acknowledged as a significant predictor of MACE. The presence of ischemia was associated with the development of MACE with an adds ratio of 3.52 and with the fatal outcomes for cardio-vascular reasons

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with an odds ratio of 2.55. LGE was also shown to be an independent predictor for unfavorable outcomes.

Adenosine is often used as a vasodilating agent during the research works on the evaluation of the prognostic value of cardiac MRI. Adenosinetriphosphate provides vasodilating and haemodynamic effects similar to the one in adenosine [24, 25]. Due to the acceptable cost and accessibility issues shown for other medicinal products, adenosinetriphosphate is widely used in the countries of the Asian-Pacific region [26–28] and in some European states [25], as well as in the Russian Federation [1, 24]. M.Y. Ng et al. [29] have arranged a research work, in which 208 patients with suspected IHD underwent stress perfusion MRI of the heart using adenosinetriphosphate. Within a mean follow-up period of 3.3 years, the patients with stress-induced ischemia had higher MACE rates. Independent predictors of developing MACE were the stress-induced ischemia (odd ratio — 3.63), the decrease in the left ventricle ejection fraction and the presence of myocardial infarction.

The absolute coronary flow reserve (CFR), defined using the phase-contrasted kinematic MRI (kin-MRI), is an excellent prognostic value for MACE and for cardiovascular-related death in patients with known or suspected IHD [30, 31]. Phase-contrasted kin-MRI allows for quantitative evaluation of the circulation in the coronary sinus, which is about 96% of the total circulation in the left ventricle [32]. By measuring the circulation in the coronary sinus, both at the stress conditions and at rest, one can calculate the total CFR, which is a ratio of the total circulation in stress to the total basal circulation in the coronary sinus.

S. Nakamura et al. [28] have investigated the auxiliary prognostic value of the stress perfusion MRI of the heart and of the CFR, measured using phase-contrasted kin-MRI, in 933 patients with suspected IHD. With the median duration of follow-up being 5.3 years, the analysis of Kaplan–Meier curves has shown a significant difference in the event-free survival between groups with the total CFR <2.5 and the absolute CFR >2.5 (p <0.001), as well as between patients with or without ischemia (p <0.001). The combination of stress perfusion MRI of the heart and the absolute CFR has significantly improved the risk stratification. The prognosis was comparable in the subgroups with ischemia and CFR >2.5 and without ischemia and CFR <2.5 (p=0.731). Thus, stress perfusion MRI of the heart and the phase-contrasted kin-MRI for the purpose of defining the absolute CFR have shown an additional prognostic value for cardio-vascular events.

The quantitative evaluation of stress perfusion by means of cardiac MRI allows for evaluating both the total stress MBF and the total flow reserve without the necessity of using the phase-contrasted MRI-visualization of the coronary sinus. K.D. Knott et al. [33] have assessed the prognostic value of the absolute stress MBF and of the MPR using the quantitative stress perfusion cardiac MRI. Their research, that included 1,049 patients with suspected IHD, has shown that both the stress MBF and the MPR were independently related to the risk of fatal outcome and MACE. In particular, the corrected odds ratios for fatal outcome and MACE were 1.93 and 2.14 for each 1 ml/g per minute of decreased stress MBF vs. 2.45 and 1.74 for each unit of MPR decrease, respectively.

The quantitative evaluation of MBF and MPR using stress perfusion cardiac MRI allows for precisely evaluating the risk in IHD patients. Updated recommendations from the American Heart Association (AHA, 2023) on managing chronic IHD encourage using the cardiac MRI for the quantitative evaluation of MBF for the purpose of improving the risk stratification [34]. The precise risk stratification with the aid of quantitative cardiac stress perfusion MRI can contribute to drawing up justified clinical decisions by means of identifying the patients, in which re-vascularization or optimal medication therapy can bring the maximal benefit.

CORONARY MICROVASCULAR DYSFUNCTION

The term «coronary microvascular dysfunction» describes a spectrum of structural and functional changes in the coronary microcirculation, leading to impaired MBF and ultimately to myocardial ischemia [35]. CMD develops due to functional and/or structural changes in the microcirculation [35]. The functional mechanisms may include impaired vasodilation and/or microvascular spasm. The impairments of vasodilation can result from endothelium-dependent and/or endothelium-independent mechanisms. The endothelium-dependent mechanisms are related to the decreased synthesis and/or accelerated degradation of nitrogen oxide (NO) and other relaxing factors, produced by the endothelium, which limits the ability of the vessels to dilate [36]. The endothelium-independent mechanisms include the impaired relaxation of the smooth muscles of the vessels and the increased reaction to vasoconstricting mediators [35]. The microvascular spasm is a part of a spectrum of vasomotor disorders and it is closely related to the dysfunction of the endothelium, in which the vasoconstricting tonus prevails [37]. The structural changes manifest as the narrowing of the lumen in the intramural arterioles and capillaries, by perivascular fibrosis, by the decreased number of capillaries and by the accumulation of the glycation end-products [38, 39].

Diagnostics of coronary microvascular dysfunction by means of stress perfusion magnetic resonance imaging of the heart

The cardiac stress perfusion MRI allows for evaluating the condition of both the epicardial coronary arteries and the microcirculation. If the patients having no impairment in the epicardial coronary arteries show impaired perfusion caused by stress, this can indicate the presence of CMD. The cardiac MRI, just like the PET, allows for quantitative determination of the MBF at rest and upon pharmacologically induced stress, which helps in precisely diagnosing the CMD. In their research, H. Rahman et al. [40] evaluated 75 patients with chest pain, but without IHD. CMD was defined by the invasive parameter — the CFR <2.5. The results have demonstrated that MPR has a high diagnostic precision (AUC 0.88) and it is superior comparing to the visual evaluation (AUC 0.60) for the diagnostics of CMD. Visual evaluation had a precision of only 58% with a sensitivity of 41% and with the specificity of 83%. A single parameter of stress MBF was proven to be insufficient for the diagnostics of CMD. The research emphasizes the importance of using the combination of stressed and basic measurements of perfusion for precise detection of CMD.

The distinction between the epicardial IHD and CMD is complicated upon visual evaluation of the cardiac stress perfusion MRI, however, the quantitative stress perfusion MRI of the heart allows for differentiating these two conditions. T. Kotecha et al. [41] have evaluated the efficiency of quantitative cardiac stress perfusion MRI in the detection of clinically significant IHD (FFR <0.80), as well as in its differential diagnostics with CMD (FFR >0.80; index microvascular resistance [IMR] <2.5). The results have demonstrated that foci with epicardial IHD had significantly lower values of MBF and MPR comparing to CMD foci and to the normal areas. The MBF values (in cases of stress) being ≤1,94 ml/g per minute were effective in detecting the clinically significant IHD, while the total MBF value (in stress) of <1.82 ml/g per minute was showing the presence of tri-vascular lesions and CMD.

The MPR index, calculated based on the cardiac MRI data (myocardial perfusion reserve index, MPRI), is a reliable semiquantitative parameter, reflecting the microvessels' ability to dilate. This parameter is calculated as the ratio of circulation increase upon loading to the increase in the circulation at rest, normalized as compared to the increase in the left ventricle circulation [42]. W. Zhou et al. [43] have investigated the long-term prognosis in CMD patients having symptoms of ischemia, but without the impairment of the epicardial coronary arteries, by means of using the semi-quantitative analysis of cardiac stress-MRI. Within a follow-up period of 5.5 years, MACE was developing in 15.6% of the patients. The risk of developing MACE in patients having the MPRI of ≤1.47 was 3 times higher than in patients with the MPRI of >1.47. The multivariate analysis has confirmed that MPRI is an independent predictor of developing MACE. The complete quantitative evaluation of the perfusion by means of cardiac MRI can provide even more precise stratification of risk. Further studies are required for the evaluation of the prognostic value of the quantitative stress perfusion cardiac MRI in CMD patients.

Diabetes mellitus and coronary microvascular dysfunction

L. Jiang et al. [44] have studied CDM in a model of streptozotocin-induced diabetes mellitus in pigs (12 animals) using the quantitative myocardial perfusion by means of cardiac MRI. The animals underwent the procedures of longitudinal quantitative perfusion MRI of the heart in 2, 6, 10 and 16 months from the beginning of the experiment. The research has shown that MPR significantly decreases eventually, which indicates the progression of CMD along with the development of the disease. The MPR decrease also correlates with the increase in fasting blood glucose and glycol-hemoglobin (HbA1c), with a decrease in the longitudinal strain of the left ventricle and with an increase in the left ventricle remodeling index. Histological examination has shown an increase in the collagen volume fraction, which indicates the development of interstitial fibrosis in the myocardium, while the density of the microvessels remained unaltered at the initial stages of diabetes mellitus [44]. These data show that the decrease of MPR occurs earlier than the changes in the microvessel density, and it is related to the structural and functional changes in the coronary microvessels.

J.L. Yeo et al. [45] have examined 205 patients with type 2 diabetes and 40 healthy volunteers as the control group. In patients with type 2 diabetes, MPR was significantly lower comparing to the control group

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(1.78±0.55 and 2.00±0.63 ml/g per minute, respectively; p=0.032). MPR in diabetic patients was also decreased comparing to the control group (2.82±0.83 vs. 3.18±0.82; p=0.020). These results allow for suggesting that CMD may play the key role in the pathogenesis of cardiomyopathy associated with type 2 diabetes mellitus in humans.

Diastolic dysfunction and diabetes mellitus

Diastolic dysfunction is widely spread worldwide and it is associated with unfavorable outcomes in patients with diabetes [46]. A.S. Bojer et al. [47] have investigated the relation of the extracellular volume (ECV) of the myocardium and the MBF with the diastolic function of the heart in patients with type 2 diabetes mellitus. The research included 205 patients with type 2 diabetes and 25 individuals of the control group, in which ECV and MBF were measured at rest and in stress along with evaluating the MPR during the cardiac MRI. An increase of the ECV, indicating the interstitial myocardial fibrosis, was independently related to the worsening of diastolic functions, in particular, with a decrease of the early peak filling rate (ePFR) and with an increase of the maximal volume of the left atrium (LAmax). The increased MBF and MPR values upon loading were related to the improvement of the diastolic function, in particular, with the improvement of the early diastolic myocardial relaxation, as indicated by the lateral parameters and by the mean E/e value. These data show that diffuse myocardial fibrosis and CMD contribute to the development of diastolic dysfunction in the left ventricle in cases of type 2 diabetes, with the myocardial fibrosis affecting the myocardial elasticity and the CMD — the early relaxation of the myocardium. This emphasizes the importance of affecting both the fibrosis and the CMD in the treatment of cardio-vascular complications in patients with type 2 diabetes.

NON-ISCHEMIC CARDIOMYOPATHY

The primary non-ischemic cardiomyopathy, such as the hypertrophic cardiomyopathy and dilated cardiomyopathy, are related with the progression of diffuse myocardial fibrosis. The use of LGE and parametric mapping of the myocardium during the cardiac MRI is considered a reliable method for the differential diagnostics of various types of cardiomyopathy, for predicting outcomes and selecting the therapeutic strategies [48–51]. A recent prospective multicenter research has shown that ECV is an independent prognostic marker, both for the cardiac failure and for the arrhythmia — related events, in patients with dilation cardiomyopathy [52]. Besides myocardial fibrosis, CMD can be the additional key abnormality in cases of non-ischemic cardiomyopathies.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by complex interactions between the cellular dysbalance, the interstitial fibrosis with thickened fibers surrounding the myocytes, the abnormalities in the mitral valve and in the sub-valvular structures of the heart, as well as the remodeling of coronary microvessels along with the hypertrophy of cardiomyocytes. These structural changes in cases of HCM serve as a basis for developing the CMD, which then leads to recurrent myocardial ischemia with the increased need of oxygen [38]. Though CMD manifests in hypertrophic or cicatricial areas of the myocardium, it can develop in the visually normal segments. The decrease of MBF without impairing the coronary arteries is a characteristic feature of HCM.

R.K. Hughes et al. [53] have arranged a case-control research, in which they evaluated the MBF and MPR among the genetically typed and HCM-positive individuals, but without the clinical hypertrophy in the left ventricle. The results have demonstrated that positive genotype individuals without hypertrophy in the left ventricle show a decrease of MPR (2.77±0.83) comparing to the control group (3.24±0.63; p=0.009), which indicates the presence of impaired MPR even in the absence of significant hypertrophy of the left ventricle and myocardial fibrosis. This confirms that CMD is present even among the HCM mutation carriers without evident clinical manifestations.

G. Joy et al. [54] have studied the microstructure of the myocardium and the functions of the microvessels by means of diffusion tensor imaging and stress perfusion, comparing these parameters in patients with the subclinical and the manifesting form of HCM, as well as in healthy volunteers. The authors have found significant differences in the microstructural characteristics between the groups compared, with the values of the fractional anisotropy being 0.32 (95% confidence interval [CI] 0.30–0.33) for subclinical forms of HCM and 0.28 (95% CI 0.25–0.30) for manifesting forms of HCM comparing to 0.34 (95% CI 0.33–0.36) in healthy individuals (p <0.001). Significant changes were also found the MBF parameters: 2.46±0.54 ml/g per minute for subclinical HCM, 1.77±0.52 ml/g per minute for manifesting HCM and

2.77±0.62 ml/g per minute in the control group (p <0.05). These significant changes within the structure of the myocardium and in the functions of the microvessels, both in cases of subclinical and manifesting HCM, may serve as a marker of early manifestations of HCM.

C.E. Raphael et al. [55] have investigated the factors predicting the development of cardiac failure in HCM, paying special attention to myocardial fibrosis and to the status of the microvessels. The authors came to the conclusion that the end-systolic volume index of the left ventricle and the degree of fibrosis in the myocardium (%LGE) are important predictors of future episodes of cardiac failure. The hazard ratio (HR) for the end-systolic volume of the left ventricle was 1.44 (95% CI: 1.16–1.78; p=0.001), while for the %LGE, calculated per each 10% of increase, — 1.44 (95% CI: 1.14–1.82; p=0.002). Within the multivariate analysis, the significant predictors of cardiac failure were the age (HR 1.37; 95% CI: 1.06–1.77; p=0.02) and the presence of mitral regurgitation (HR 2.6; p=0.02). With this, the presence or the degree of induced perfusion defect according to visual evaluation were not related with the outcomes (p=0.16 and p=0.27 respectively).

The quality of myocardial perfusion itself is not considered a predictor of developing cardiac failure. Quantitative perfusion MRI of the heart can become more informative for detecting CMD in cases of HCM, but additional research works are required for the evaluation of its prognostic role in HCM patients.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by an increase in the dimensions of the left ventricle and by the decrease in its contractile functions, with this, there are no signs of significant stenosis in the coronary arteries [56]. Despite the absence of classic IHD, several research works in the filed of nuclear medicine have revealed a decrease of MPR in DCM patients, which may indicate the presence of CMD as the main cause of the disease [57–59]. Though DCM is traditionally considered a non-ischemic form of cardiomyopathy, these data suggest that chronic or recurrent hypoperfusion of the myocardium may lead to myocardial fibrosis and remodeling in cases of DCM [59–61].

A. Gulati et al. [61] have investigated the interrelation between the stress perfusion parameters, MBF and MPR, along with the remodeling of the left ventricle, in DCM patients. The research work included a quantitative evaluation of the MBF parameters at rest and in stress among 65 DCM patients comparing to 35 healthy volunteers of the control group. The results have demonstrated that, in DCM patients, the total MBF at rest was significantly higher comparing to the healthy volunteers, but the total MBF measured during stress was decreased, resulting in an alteration of MPR. Besides, the MBF during stress and the MPR were significantly decreased in patients with the left ventricle ejection fraction ≤35% comparing to the patients with the LV ejection fraction being >35%. The segments of the myocardium with LGE at rest and during stress had lower MBF values comparing to the segments showing no LGE.

M. Takafuji et al. [62] have compared the absolute CFR values measured using the phase-contrasted MRI, in 26 DCM patients and 26 healthy individuals. The results have demonstrated that the total CFR was significantly lower in DCM patients (2.87±0.86) comparing to the control group (4.03±1.47; p=0.001). The multicomponent linear regression analysis has revealed that global longitudinal deformation of the left ventricle (global longitudinal strain, GLS) is the only independent predictor of the total CFR (β=-0.558, p=0.003). These data confirm the hypothesis that CMD in cases of DCM promotes to subendocardial hypoperfusion, affecting the longitudinal structure of the myocardium and decreasing the GLS.

Despite the fact that previous trials have provided the convincing evidence of the relation between DCM and CMD, larger prospective research works are necessary for investigating the correlations between CMD and myocardial fibrosis in DCM patients.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome, which is accompanied by symptoms and signs of heart failure, despite the normal or almost normal ejection fraction of the left ventricle [63]. The diastolic dysfunction is the key hemodynamical component of HFpEF. This process is characterized by the unfavorable remodeling of the left ventricle, by cardiometabolic dysfunction and by interstitial myocardial fibrosis. Besides, CMD can play an important role in the pathogenesis of HFpEF [64, 65]. A recent research work on PROM-HFpEF has shown that 75% of the HFpEF patients had CMD (CFR index <2.5 during Doppler echocardiography) [66, 67]. In a pre-planned DIAMOND-HFpEF trial that was assessing the CMD in HFpEF patients using cardiac MRI, it was found that CMD (MPR <2.0) was revealed

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in 70% of the HFpEF patients comparing to 48% in the control group. CMD was associated with the worst clinical outcomes, such as increased mortality and hospitalization rates in HFpEF patients. The research work also did not reveal any significant correlation between MPR and myocardial fibrosis, which allows for suggesting that CMD and fibrosis may independently affect the pathophysiology of HFpEF [68].

C. Siggins et al. [69] have investigated the interrelation between various biomarkers and cardiac MRI parameters in 19 HFpEF patients and in 15 healthy volunteers of the control group. The multiparametric analysis of cardiac MRI data and of the biomarkers has revealed 7 such factors which significantly correlate with ECV, and 6 — with MPR, however, only one biomarker was significantly correlating both with the ECV and with the MPR. The results have demonstrated that myocardial fibrosis and CMD may manifest differently in HFpEF patients. This observation has allowed for suggesting that the metabolic syndrome, the kidney diseases and the systemic inflammation may take part in the development of myocardial fibrosis and chronic heart failure [69].

PROBLEMS AND PERSPECTIVES OF QUANTITATIVE PERFUSION MAGNETIC RESONANCE IMAGING OF THE HEART

Quantitative perfusion MRI of the heart represents a modern method of evaluating the MBF and MPR with high spatial and temporal resolution capability. Unlike the qualitative perfusion MRI, based on the subjective visual evaluation of perfusion defects, quantitative MRI allows for measuring the absolute circulation parameters in milliliters per gram of myocardium per minute (ml/g per minute), which significantly increases the precision of diagnostics and reduces the effects of the human factor [70].

The main stages of quantitative perfusion MRI are the following:

- administration of contrasting agent (gadolinium-based);
- dynamic scanning with high frame rate for the evaluation of the contrasting agent entering the myocardium;
- analyzing the time of transit for the contrasting agent in the myocardium by means of kinetic modeling;
- calculating the absolute MBF values at rest and upon pharmacologically induced stress (usually with adenosine or regadenoson);
- evaluation of the MPR as the ratio of MBF in stress to the MBF at rest.

Clinical application of quantitative perfusion magnetic resonance imaging

Evaluation of the ischemic heart disease. The quantitative perfusion MRI, allowing for highly precise detection of hemodynamically significant stenoses of the epicardial coronary arteries, is comparable to the invasive coronary angiograph and FFR. In the CE-MARC research, the quantitative MRI has shown a sensitivity of 86% and a specificity of 83% in the diagnostics of IHD, which is comparable to SPECT and PET [3, 4, 15].

Detection of coronary microvascular dysfunction. CMD is characterized by impaired myocardial perfusion in the absence of significant stenoses in the coronary arteries. Quantitative MRI allows for precise diagnosing the CMD, measuring the MBF and MPR. The MPR values of <2.0 indicate the presence of microvascular impairment and may be used for predicting the unfavorable cardio-vascular events.

Risk stratification in patients with cardio-vascular diseases. Quantitative perfusion MRI has a high prognostic value. In the SPINS trial including patients with normal MBF values and with the absence of LGE, the five-years survival rate was >99%, while in patients with a significant MBF decrease, the risk of serious cardio-vascular events was increasing 4-fold [20].

The quantitative perfusion MRI of the heart has shown a significant potential in the diagnostics, in developing therapeutic strategies and in predicting various cardio-vascular diseases, especially after the implementation of methods for creating the high-quality images and quantitative evaluation of myocardial perfusion [70]. Recent research works emphasize a vast potential of this method in the settings of its wide use in medical practice, however, for the successful transition from scientific research to everyday clinical practice, it is necessary to solve several key tasks.

1. Absence of unified standards for processing the data and processing the results.

   One of the main problems is the absence of unified standards for data collection and further processing of information. For example, the saturation in T1 mode occurs in the left ventricle, when the concentration of the contrasting agent exceeds a certain value during the first injection of gadolinium, but in the myocardium this effect can be insignificant. In order to manage this, two basic approaches are used — the double-bolt method and the method of double sequence, which help avoiding the excessive saturation of the left ventricle and preventing the artifacts occurring during the first injection of the contrasting agent. However, despite this, the problem remains topical, for there are differences in the platforms from various CMR manufacturers, in the voltages of the magnetic field, in the contrast infusion protocols, in the scanning settings and in the post-processing methods, including the algorithms of kinetic modeling.

2. The non-coordination in quantitative parameters of MBF.
   Various cardiac MRI platforms may show different MBF values, which complicates clinical interpretation and decision-making. It is necessary to draft a unified standard for the evaluation of circulation, which shall allow for eliminating these differences and for increasing the diagnostic precision.
3. Variability of MBF changes.
   There is a high variability in MBF measurements, which affects the precision of diagnostics and can depend on various factors, such as the operator skills, the experience of using specific software, the quality of the software itself and the operating conditions of the equipment. The solutions for this problem can include the operator training programs, the standardization of protocols and the development of automated data processing systems.
4. Incorrect circulation kinetics models.
   There are multiple various kinetic models for the evaluation of circulation, each one providing various results. The selection of the optimal model is a difficult task, requiring thorough analysis and testing. This problem is aggravated by the absence of consensus opinion on the best model for quantitative evaluation of circulation.
5. The necessity of a reliable validation system.
   For increasing the reliability and precision of the quantitative perfusion MRI of the heart, a validation system is required, which should include the verification of kinetic models, the verification of MBF measurement accuracy and the standardization of data processing protocols.
6. Improper data processing.
   Its is necessary to develop a reliable system for the storage and processing of data, which shall provide the accurate preservation and reproduction of the information acquired by means of cardiac MRI. Automated data processing systems can help minimizing the errors and increasing the precision of the analysis.
7. Developing the software tools based on artificial intelligence.
   Using the cutting-edge technologies of artificial intelligence, such as machine learning, can help decreasing the variability and increasing the accuracy of measurements, especially when processing large data sets.
8. Support from the experts.
   Arranging the training sessions for specialists and providing support from the experts play an important role in the successful implementation of cardiac MRI in clinical practice. Standardized courses and trends can help training the qualified personnel, which promotes to the effective operation when using the new technologies.
9. Solving the problems of training and certification.
   Arranging specialized courses and training programs can help solving the problem of the lack of qualified staff, capable of operating this new technology. Developing a system of accreditation exams is also important for confirming the qualification of a specialists.

The prespectives of quantitative perfusion magnetic resonance imaging

The promising trends of development in this field include the following:

- automation of the analysis using artificial intelligence (algorithms of machine learning shall allow for standardizing data processing and reducing the variability);
- integration with other MRI methods (combination of quantitative perfusion with T1/T2-mapping and phase-contrasted kin-MRI improves the combined evaluation of the myocardium);
- developing new contrasting agents (using ferumoxytol instead of gadolinium in patients with renal failure);
- implementation of testing standards (introducing the international reference values for MBF and MPR shall allow for increasing the reproducibility of the method);
- expanding the clinical indications (using this method in cases of cardiomyopathy, inflammatory heart diseases and post-Covid complications).

The quantitative perfusion MRI of the heart is a promising tool for diagnostics and for risk stratification in cases of cardio-vascular diseases. Its implementation is especially important for detecting the CMD, for assessing the severity of ischemia and for predicting the outcomes, however, for the successful integration of the method into clinical practice, there is a need for overcoming the elimination of technical limitations along with the analysis standardization and with the automatization of data processing.

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CONCLUSION

The quantitative evaluation of cardiac perfusion MRI provides a possibility of objective and precise diagnosing the IHD, also allowing for better recognition of CMD, which previously was difficult to evaluate when using qualitative visual evaluation. Quantitative perfusion MRI of the heart also provides a more precise prognostic stratification for various heart diseases, including the hypertrophic cardiomyopathy, the dilated cardiomyopathy and the heart failure with preserved ejection fraction, which is an additional capability in understanding the pathophysiology underlying the non-ischemic cardiomyopathies, such as the hypertrophic cardiomyopathy and dilated cardiomyopathy, as well as the cardiac failure with preserved ejection fraction. The quantitative MRI of myocardial perfusion, especially when combined with functional evaluation of the MRI data and with determining the characteristics of the tissues, can aid in more detailed investigation of the coronary macro- and microcirculation, which shall promote to better understanding of the nature of myocardial ischemia.

ADDITIONAL INFORMATION

Author contribution. *E.R. Pogrebnichenko* — concept and design of the study, data analysis, writing the article; *A.S. Mameshova*, *Z.A. Akhmedbekova*, *P.T. Tedurova* — collection of material, data processing, statistical analysis; *M.A. Kamilov* — manuscript critical revision; *E.A. Alibekov*, *K.M. Gazimagomedov*, *Ch.S. Saipullaev*, *N.Yu. Popov*, *A.L. Abdulaev* — interpretation of results, participation in discussion and editing of the manuscript; *Kh.S. Nasueva* — methodological support, coordination of group work; *M.M. Bakarova*, *Z.V. Erkenova* — technical editing of the article, search and analysis of data. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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