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REVIEW ARTICLE

Detection of viable myocardium in patients with ischemic myocardial dysfunction: modern possibilities and practical value

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Summary

This article observes modern methods of viable myocardium detection in patients with ischemic heart disease. The article reviews diagnostic possibilities of positron emission tomography, single-photon emission tomography, cardiovascular magnetic resonance and stress echocardiography and describes the role of viability imaging in current clinical practice. Viability testing along with a number of clinical factors plays a key role in the treatment of patients with ischemic myocardial dysfunction. This article discusses the results of clinical studies dedicated to the study of evaluation of the viable myocardium before myocardial revascularization. The review observes literature data demonstrating that cardiac resynchronization therapy inefficacy might be related to the lack of viable myocardium at the segments targeted by the left ventricle lead.

Keywords

Ischemic myocardial dysfunction, myocardial viability, nuclear imaging, magnetic resonance, stress echocardiography.

Despite the progress of medical science, coronary heart disease (CHD) and myocardial dysfunction caused by it remain an important problem of modern cardiology [1, 2]. Myocardial dysfunction together with its structural remodeling and several neurohormonal systems activations are the key pathogenetic elements of heart failure progression and development [2].

It has been proved that myocardial contractility reduction is connected not only with scar changes but also with reversible myocardial dysfunction [3]. These myocardial areas contrain cardiomyocytes that do not contract actively but maintain minimal oxygen consumption and main cellular metabolism components, so they stay "alive", but at the same time are kept in reserve [4]. Therefore, influencing reversible dysfunction can become a promising direction of pharmaco-

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logical and surgical treatment [5]. This consideration makes it important to detect viable myocardium.

There are two forms of myocardial ischemic dysfunction with potentially reversible contractility reduction: hibernation and stunning [6, 7]. The difference between these variants appears after myocardial blood flow estimation: in hibernation blood flow in rest is reduced, whereas in chronic stunning the blood flow in rest can be preserved, but blood flow reserve is lowered [8].

In practice stunning and hibernation can coexist and it is not necessary to differentiate them, since both types of myocardial dysfunction are reversible, both when after blood flow is reestablished and after the normalization of balance between oxygen delivery and consumption by myocardium [9]. The presence of preserved cellular metabolism and contractility reserve allowed to unite the variants of reversible cardiac muscle dysfunction under the term "viable myocardium" [10].

Main viable myocardium characteristics (Table 1) like the presence of contractility reserve and metabolic activity, preserved perfusion and cardiomyocyte cell membrane integrity underlie its non-invasive diagnostics using various techniques of cardiovascular visualization [11]. It is also possible to detect viability of dysfunctional myocardium indirectly excluding nonviable (scar) tissue [12].

Table 1. **Viable myocardium diagnostic techniques**

Diagnostic principle	Diagnostic technique
Evidences of the presence of myocardial metabolic activity	Positron emission tomography (PET) of the heart with fluorodeoxyglucose
Estimation of myocardial perfusion and cardiomyocyte cell membrane integrity	Radioisotope heart scan – single photon emission computer tomography (SPECT) with ^{201}Tl and ^{99m}Tc-containing drugs.
Detection of myocardial contractility reserve	Stress-echography with dobutamine, dobutamine stress magnetic resonance imaging (MRI)
Evidence of the presence of viable myocardium excluding non viable (scar) tissue	Heart MRI with contrast use

Cardiac PET

Nowadays PET is taking the key role in viable myocardium diagnostics. PET is based on the use of radiopharmaceuticals (RP) tagged with isotopes – positron emitters [13]. Unlike traditional techniques of nuclear medicine, RP used in PET are made of isotopes of important biological atoms and molecules (oxygen, carbon, nitrogen, glucose) that are natural metabolites of organism [14, 15]. PET images reflect RP distribution in examined organ and allow to estimate cellular metabolism, blood flow and myocardial perfusion [15, 16]. Introduction of hybrid scanners that unite PET and computer tomography (CT) (PET/CT) and MRI (PET/MRI) can give additional opportunities for complex estimation of structural and functional heart changes in patients with coronary pathology [13].

18-fluorodeoxyglucose (^{18}F-FDG) is used as a RP for viable myocardium detection in PET [14]. Modern estimation of myocardial perfusion and glucose consumption in different myocardial segments allows to detect both nonviable myocardium areas (scar tissue) – lowered perfusion and glucose intake – and viable tissue – normal or elevated glucose consumption in lowered perfusion zone [16].

Estimation of perfusion in viable myocardium diagnostics

Radioisotope techniques of perfusion estimation can be used for viable myocardium detection (myocardial perfusion scintigraphy, SPECT) [17]. These methods are based on estimation of intravenously administered RP distribution in cardiac muscle that enters undamaged cardiomyocytes proportionally with coronary blood flow [11]. Myocardial parts with normal perfusion create the image of homogenous RP distribution, whereas myocardial zones with relative or absolute blood flow reduction due to ischemia or scar damage have lowered RP incorporation in place of perfusion defects [17]. RP distribution in myocardium depends on perfusion by itself, sarcolemma integrity and preserved cellular metabolism [11]. Nowadays thallium chloride (^{201}Tl) and technetium-based drugs (^{99m}Tc) are main RP for estimation of perfusion in SPECT [18].

Thallium chloride ^{201}Tl, biological analogue of potassium, that enters cardiomyocytes like potassium through Na+/K+ ATPase [18]. Early distribution pattern is proportional to blood flow, whereas late distribution pattern indicates the tissue with undamaged intra/extracellular gradient, which allows to differentiate viable and nonviable (scar) myocardium [11, 19].

Two separate injections are used for ^{99m}Tc-labeled RP since these drugs do not allow to determine redistribution in myocardium after single administration [18, 20]. Viable myocardium diagnostics in this case is performed using nitroglycerine test [21]. There are some data about possible use of ^{99m}Tc-labeled RP in SPECT combined with pharmacological dobutamine test [22].

Fatty acids labeled with iodine-123 (^{123}I) are considered to be another RP for viable myocardium detection [23]. Their mechanism of action, unlike perfu-

sion agents, is directed to myocardium metabolism estimation [24]. Normal myocardium metabolizes fatty acids instead of glucose, whereas myocardial segments with reversible dysfunction consume glucose that causes defects in fatty acids perfusion [25]. Combined use of RP for estimation of perfusion and metabolism allows detecting the difference between the condition of perfusion and metabolism in the same zones of the heart – so-called perfusion-metabolic discrepancy which corresponds with viable myocardium zones [24, 26].

Stress-echography in viable myocardium diagnostics

Examination of myocardial systolic function using echography in rest does not allow to determine if the segments with impaired kinetics can be considered as viable or scar tissure [27]. The only exception is improvement of viable myocardial segments contractility after postextrasystolic contraction [28, 29].

The presence of positive inotropic reserve that is expressed as increased contractility in response to inotropic stimulation is an important feature of reversible myocardial dysfunction [30].

This sign allows to stress-echocardiography for viable myocardium verification [11]. Unlike it, nonviable myocardium (scar) would not improve contractility (negative inotropic reserve) [31].

Tests with pharmacological agents that either increase contractility (dobutamine 5-10 μg/kg/min) or redistribute coronary blood flow causing coronary steal syndrome (dipyridamole 0.28 mg/kg) are used to identify viable myocardium during stress-echocardiography [11].

Techniques based on tissue dopplerography that analyze velocity of motion, deformation speed and myocardial deformation are used for regional myocardial kinetics estimation [32, 33, 34]. Despite obvious advantages comparing with semi-quantitative estimation of regional kinetics in echography, these techniques based on Doppler's effect have several limitations: their result depends on angle of scanning, movement of adjacent myocardial areas and heart movements by themselves cause errors in measurements [11].

During the last years the analysis of myocardial deformation with speckle-tracking technique is used in stress-echocardiography for quantitative estimation of myocardial kinetics [35]. This technique is not based on Doppler's effect, that's why it has no disadvantages of tissue dopplerography [36]. Several studies demonstrated high informativeness of this method for detection not only viable myocardium, but also scar tissue [37].

Heart MRI in viable myocardium diagnostics

Heart MRI with dobutamine test can be used for viable myocardium diagnostics [38]. Stress MRI with dobutamine test is based on the same principles of contractility reserve estimation as stress-echocardiography and is performed according with a similar protocol. At the same time stress MRI has the advantage of high spatial resolution and reproducibility comparing with stress-echocardiography [38].

Another way to distinguish reversible and irreversible myocardial damage using gadolinium chelates as contrast agents is MRI [39, 40]. In this case paramagnetic contrast agent based on gadolinium is accumulated in necrotic nonviable myocardium [12]. Possible cause of scar-changed myocardium contrasting can be the change of gadolinium kinetics due to increased volume of extracellular fluid because of damage of cardiomyocyte membreanes. High spatial resolution, possibility to obtain information without stress test and absence of radiation exposure are the advantages of contrast-enhanced MRI [40].

Viable myocardium diagnostics before revascularization operations in left ventricle (LV) ischemic dysfunction

Surgical myocardial revascularization is widely used in patients with CHD [41]. According with the modern guidelines, the decision about revascularization should be based on verification of significant coronary arteries stenosis, degree of ischemia caused by it and estimation of expected benefit for prognosis and/or improvement of clinical symptoms [42]. One of important predictors of coronary bypass grafting surgery (CBGS) efficacy is LV dysfunction [43]. It has been shown that CBGS promotes more significant improvement of CHD patients' survival in case of more severe manifestations and presence of LV dysfunction [42].

At the same time patients with severe LV dysfunction (LV ejection fraction <35%) and heart failure are the most difficult category of patients with CHD from myocardial revascularization point of view due to increased perioperative mortality [41]. Therefore, viable myocardium detection in these patients could in theory increase treatment efficacy. More than 100 nonrandomized studies that involved more than 3 thousands patients have proved it. Prognostic precision of

Table 2. **Prediction of global contractility improvement after revascularization using different viable myocardium diagnostic techniques (J.J. Bax andV. Delgado, 2015)**

Method	Number of studies	Number of patients	Sensitivity, %	Specificity, %
PET with ^{18}F-FDG	24	756	92	63
^{201}Tl	40	1119	87	54
^{99m}Tc	25	721	83	65
Stress-echocardiography with dobutamine	41	1421	80	78
Stress-MRI with dobutamine	9	272	74	82
Contrast-enhanced MRI	5	178	84	63

different viable myocardium diagnostic methods for improvement of global contractility after revascularization according with the results of main observation studies [44] is demonstrated in the Table 2.

Meta-analysis of 24 studies that involved in total 3088 persons with ischemic systolic LV dysfunction, demonstrated that patients with viable myocardium who took pharmacological treatment had the highest mortality rate between all subgroups. At the same time, if there was viable myocardium relative mortality reduction in case of revascularization comparing with pharmacological treatment was around 80%, and in case of its absence relative mortality reduction was 51% [45]. Other studies had similar results together with the possibility to detect viability for prediction of regional and global LV systolic function improvement and increased stress tolerance after revascularization [46].

However the results of major multicenter studies PARR-2 (The PET and Recovery Following Revascularization) and STICH (Surgical Treatment of IsChemic Heart failure) that estimated myocardium viability in patients with CHD were controversial.

Multicenter randomized trial PARR-2 involved 428 patients with LV ejection fraction <35% and suspected CHD that had been randomized into the groups where revascularization was planned according with viable myocardium diagnostics using PET with ^{18}F-FDG and where viable myocardium verification was not considered crucial for treatment tactics [47].

Results of PARR-2 study did not demonstrate significant reduction of cardiac events in patients for whom the decision about revascularization was based on results of viable myocardium tests comparing with the group of standard referral to vascularization. After one year the percentage of patients who survived one of endpoints (cardiac death, myocardial infarction, admission to hospital due to heart pathology) was 30% in "PET strategy" group versus 36% in "standard treatment strategy" group (relative risk 0.82%, 95% confidence interval (CI) 0.59-1.14; p=0.16) [47].

It is necessary to keep in mind that in this study there were deviations from treatment strategy based on PET results in 25% of cases [48]. In particular, the main reasons to renounce revascularization were cardiac events, comorbidity and renal failure [47].

At the same time PARR-2 study revealed significant differences of RR between patient referred and not referred to revascularization after PET diagnostics of viable myocardium (RR=0.62; 95% CI 0.42-0.93; p=0.019) [47]. More than that, significant reduction of cardiac death was obtained in the group of patients with LV systolic dysfunction referred for revascularization due to the presence of viable myocardium without preceding coronary angiography comparing with the patients who previously underwent coronary angiography. Patients who underwent viable myocardium diagnostics without coronary angiography were characterized with lower LV ejection fraction: 25.5±7.6 vs 27.5±7.7 (p<0.01) [47]. These results demonstrate that PET can be useful for optimal selection of patients with severe LV systolic dysfunction for revascularization and also to reduce the necessity of coronary angiography performing in case if there are no evidences of viable myocardium presence.

One of directions of multicenter randomized trial STICH was dedicated to the efficacy of viable myocardium evaluation for survival prognosis in patients with CHD and LV dysfunction before CBGS [44]. 1212 patients had been involved into this study, 601 patients underwent viable myocardium diagnostics using stress-echocardiography with dobutamine, SPECT or both techniques. These patients had been randomized into two groups: pharmacological treatment and CBGS (n=298) and only pharmacological treatment (n=303) [49].

As it was expected, mortality rate was significantly higher in patients without viable myocardium (51%) comparing with the patients who had viable myocardium (37%) (RR=0.64; 95% CI 0.48-0.86; p=0.003) [49]. However the connection between the presence of viable myocardium and mortality appeared to be non-significant (p=0.21) after the correction for other initial

parameters (LV ejection fraction, LV volumes, intensity of symptoms, signs of more severe disease) [49].

Although the STICH study had been organized in quite precise way, there were several features of its design that could have affected the results.

First of all, myocardial viability had been estimated not in all patients. Consequently, natural distribution of viable and non-viable myocardium zones could have been not respected in this category of patients.

In the second place, viable myocardium diagnostics has been performed using different methods: stress-echocardiography and SPECT with ^{99}Tc, they have different underlying principles and different diagnostic value. More than that, the most sensitive technique of viable myocardium diagnostics – PET with ^{18}F-FDG – and the most precise method of scar detection – contrast-enhanced MRI– have not been used.

Thirdly, this study took into account just the fact of viable myocardium presence and not its volume. Although the results indicating that global LV function can be restored only if liminal volume of viable myocardium is present are actively discussed nowadays.

Finally, the results of viable myocardium diagnostics in the STICH study did not influence on the choice of treatment method, unlike the PARR-2 study discussed above.

Taking into account all existing limitations of this study, its results cannot be considered as a sufficient reason to refuse viable myocardium diagnostics [44]. Absence of strong correlations between myocardium viability and CBGS benefit in this study can indicate that the choice of treatment tactics in patients with ischemic systolic LV dysfunction should be based not only viable myocardium diagnostics, but also on estimation of a wider range of factors (dimensions, LV shape, etc).

The results of performed multicenter and observation randomized studies allowed to the experts of European Society of Cardiology (ESC) and European Association for Cardio-Thoracic surgery (EACTS) to select myocardial revascularization in patients with CHD and LV systolic dysfunction (LV ejection fraction <35%) only in case of viable myocardium presence as a IIa class of recommendations with B level of evidence [41].

Viable myocardium diagnostics before cardiac resynchronization therapy

During the last years cardiac resynchronization therapy (CRT), an electrophysiological method of chronic heart failure treatment based on biventricular electrical cardiac stimulation, has become widespread. Numerous multicenter studies have proved the positive effect of CRT on hemodynamics, life quality, physical exercise tolerability and prognosis in patients with severe chronic heart failure (III-IV functional class) with low ejection fraction (<35%), enlarged LV and the presence of electrical dyssynchrony (QRS>120 ms) [50, 51].

However in case of standard selection of patients for CRT the efficacy of treatment of up to 30% of patients can remain low [52]. This is so-called category of patients not responding to this kind of heart failure treatment (non-responders). Because of this new approaches for selection of patients for CRT have been developed during the last years [53]. It has been shown that the electrode for LV electrical stimulation should be located in the place of the latest mechanical activation and outside the scar area [54]. Consequently, viable myocardium verification (lack of scar changes) in patients with cardiac failure of ischemic genesis can be an objective of patients' investigation before planned intervention.

Echocardiography estimation of myocardial deformation using speckle-tracking technique [54, 55] and myocardial perfusion analysis using SPECT [56, 57] are considered as techniques allowing to define optimal position of left ventricular electrode based on scar zones detection in patients who are supposed to be referred to CRT.

Conclusion

Viable myocardium detection in patients with LV ischemic dysfunction is an important problem of clinical medicine that has been reflected in European guidelines on myocardium revascularization. The presence of viable myocardium gives a chance for using such effective treatment methods like CBGS and CRT. At the same time the results of major studies make it possible to suggest individual decision on each patient individually taking into account other clinical factors.

Modern cardiology provides many highly informative techniques for viable myocardium detection. At the same time it is necessary to perform additional prospective clinical studies to find the role of these techniques in complex examination of patients with LV ischemic dysfunction.

Conflict of interest: None declared

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