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REVIEW

MYOCARDIAL VIABILITY – AN IMPORTANT DECISION MAKING FACTOR IN THE TREATMENT PROTOCOL FOR PATIENTS WITH ISCHEMIC HEART DISEASE

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Abstract. *Ischemic heart disease (IHD) affects > 110 million individuals worldwide and represents an important contributor to the rise in the prevalence of heart failure and the associated mortality and morbidity. Despite modern therapies, up to one-third of patients with acute myocardial infarction would develop heart failure. IHD is a pathologic condition of the myocardium resulting from the imbalance in a given moment between its oxygen demands and the actual perfusion. Acute and chronic forms of the disease may potentially lead to extensive and permanent damage of the cardiac muscle. From a clinical point of view, determination of the still viable extent of myocardium is crucial for the therapeutic protocol – since ischemia is the underlying cause, then revascularization should provide for a better prognosis. Different methods for evaluation of myocardial viability have been described – each one presenting some advantages over the others, being, in the same time, inferior in some respects. The review offers a relatively comprehensive overview of methods available for determining myocardial viability.*

Key words: *myocardial viability, factor, treatment, IHD*

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Ischemic heart disease (IHD) affects > 110 million individuals worldwide and its prevalence increased by 73.3% from 1990 to 2015 [1]. It is an important contributor to the rise in the prevalence of heart failure and in associated mortality and morbidity – despite modern therapies, up to one-third of patients with acute myocardial infarction (AMI) would develop heart failure [2, 3].

IHD is a pathologic condition of the myocardium resulting from the imbalance between its oxygen demands in a given moment and the actual perfusion in the same time. Acute coronary syndromes represent-

ing imminent life-threatening conditions (e.g. AMI, unstable angina), as well as several chronic forms of the disease (e.g. stable angina, silent ischemia) have been described – each one of them potentially leading to extensive and permanent damage of the cardiac muscle.

MYOCARDIAL ISCHEMIA – EVOLUTION OF CARDIOMYOCYTE DAMAGE

Ischemia resulting from the demands/perfusion imbalance leads to inadequate blood delivery of glucose for anaerobic glycolysis, thus to insufficient adenosine triphosphate production for maintenance of transmembrane ionic gradients. In the same time, the byproduct (lactic acid) of ischemic glucose utilization is not washed away, and the resulting acidosis worsens additionally myocardial metabolism.

Recurrent episodes of short-lasting ischemia as well as prolonged ones can lead to reversible/irreversible injury of cells responsible for the generation of contractile force of the heart.

The so called *stunned myocardium* is caused by abrupt, but transient (lasting less than 30 min) severe ischemia – the resulting contractile dysfunction persists even after blood flow is restored [4]. From a morphological point of view, this form of reversible myocardial damage is characterized by lack of extracellular involvement, although repetitive stunning causes the cardiomyocytes to undergo structural changes: loss of contractile apparatus, sarcoplasmic reticulum, and T-tubules and increased glycogen plaques [5, 6]. These changes may eventually become irreversible [7]. Improvement in cardiac function is also possible, but occurs some time after cessation of ischemia [5].

Myocardial hibernation – a term used first by Rahimtoola over 30 years ago [8] was introduced for description of the chronically hypocontractile state following longer episodes of ischemia. Revascularization improves the hibernating state by delivering adequate oxygen for beta-oxidation of fatty acids [9].

Progression to irreversible cell damage involves loss of mitochondrial function, apoptosis, and expansion of the extracellular space. In such a non-viable myocardial scar specific restructuration leads to remodeling, and an association with increased risk of sudden cardiac death has been described [10].

Myocardial viability can be defined at cellular, metabolic, and functional levels. Both stunned and hibernated myocardiums are characterized by contractile dysfunction, but both consist of cardiomyocytes that are still “alive”. In the case of hibernated myocardium, the underperfused but viable tissue is salvageable, and functional improvement can occur with carefully elaborated protocols including revascularization/pharmacotherapy or a combination of both [11].

Therapeutic protocols for patients suffering from heart failure due to IHD have all a common goal – to improve longevity and quality of life. At the same time, the choice of the specific approach can be crucial for the final outcome, thus requiring careful consideration when choosing between conservative treatment (pharmacotherapy) and invasive revascularization – usually with coronary artery bypass graft surgery (CABG). Accurate determination of the degree of myocardial viability contributes to the correct selection of patients suitable for each of these management options.

The review offers a relatively comprehensive overview of methods available for determining myocardial viability.

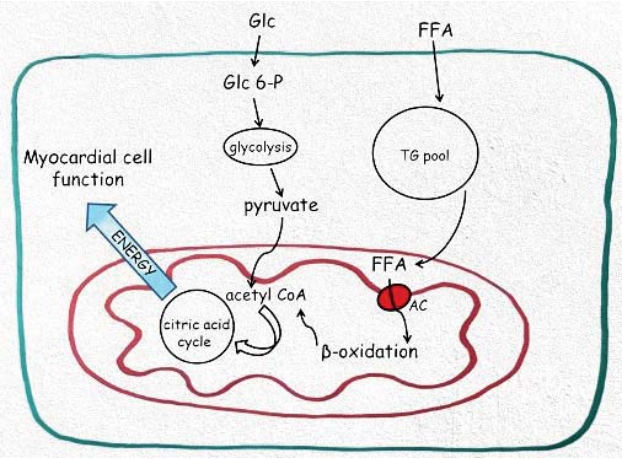
Before describing methods evaluating myocardial viability, a brief view on myocardial metabolism will be offered – understanding the differences in myocardial metabolism during resting conditions and physical activity is important for the results’ interpretation.

MYOCARDIAL METABOLISM

The main function of the myocardium – contraction, is an active process requiring large amounts of energy production in the cardiomyocytes. The sources of energy for this process are different depending on the functional state of the body and the heart.

In the postprandial state and in conditions of sufficient oxygen supply, free fatty acids (FFAs) are the “preferred” source of energy. However, with increased myocardial requirements (physical or psychological stress), glycogen stores are “encroached upon” with subsequent oxidation of glucose (Glc) and lactate (Fig. 1).

The heart represents a “metabolic omnivore” – readily switching from one energy source to another, depending on the substrate availability, coronary blood flow, oxygen supply, circulating hormones, and workload of the heart. Changes in gene expression have been shown to contribute to the ability of the heart to select the optimal metabolite for the specific moment, which is called “metabolic flexibility”. In a few words, the most efficient substrate for the moment inhibits the utilization of the non-optimal-for-the-moment substrates: FFAs inhibit Glc oxidation, and in turn Glc inhibits FFAs oxidation. Metabolic signals act as allosteric regulators of key metabolic enzymes. The preserved metabolic flexibility in the healthy heart allows its adequate adaption to increased functional demands (physical or psychological stress) [12, 13, 14].



AC – carnitine-acylcarnitine translocase, Glc – glucose; FFA – free fatty acids, TG – triglycerides

Fig. 1. Myocardial metabolism. Explanations are given in the text

Imbalance between oxygen supply and demands lies at the base of "ischemic myocardium". The heart adapts to the reduced oxygen availability through various mechanisms, and such an adaptation involves loss of the normal metabolic flexibility: in the hypertrophic and failing heart a switch in substrate preference from FFAs to Glc is often observed [15, 16]. Several mechanisms have been proposed to explain such a switch (for a review see [17]), and some authors have even suggested a switch to foetal heart gene programme [18, 19].

Acute increases in the demands increase the oxidation of glycogen, lactate, and glucose, and metabolic changes are due to increased/decreased activity of specific enzymes [20, 21, 22, 23, 24]. This ultimately potentiates glycolysis delivering acetyl-CoA for ATP production to the tricarboxylic acid cycle.

With chronically reduced oxygen supply, gene expression is affected – genes for the synthesis of enzymes and proteins involved in specific metabolic pathways are regulated at the transcriptional level. Loss of metabolic flexibility occurs early in ischemic situations – it precedes loss of contractility and is regarded as a process of impaired adaptation [12].

MYOCARDIAL VIABILITY EVALUATION

Ischemic cardiomyopathy results from the combination of a scar with fibrosis replacement and areas of dysfunctional but viable myocardium that may improve contractile function following revascularization. The assessment of viable myocardium is important for clinical practice – its presence or absence in certain quantities may give priority to one or another therapeutic approach. Observational studies reported that only patients with substantial amounts of myocardial viability had better outcomes following surgical revascularization. Yet, prospective trials have not decisively confirmed the interaction between myocardial viability and the beneficial effect of revascularization [25].

The four most widely used methods in modern clinical practice for detection of myocardial viability are dobutamine echocardiography, cardiac magnetic resonance imaging, single-photon emission computed tomography, and positron emission tomography.

DOBUTAMINE STRESS ECHOCARDIOGRAPHY (DSE)

DSE is a non-nuclear medicine method assessing myocardial viability – it does not produce ionizing radiation, using a rather widespread and readily available technique. The method describes primarily myocardial function and, to some extent, morphology, but gives also an idea about myocardial contractile reserve. Low-dose dobutamine (2.5-10 μg/kg/min) improves wall motion in the hypokinetic/akinetic regions, predicting eventual functional recovery after revascularization. Regional endocardial motion and local wall thickening in viable but acontractile segments can be visualized by a trained operator [26]. Additionally, two-dimensional speckle tracking echocardiography has been developed for easier assessment of regional myocardial deformation [27], left ventricular (LV) function in patients with ischemic LV failure [28], and hypertrophic cardiomyopathy [29].

Although crucial to clinical decision-making, echocardiographic assessment of regional LV function based on qualitative visual analysis is observer-dependent [30] and confined mainly to the morphologic characteristics of the myocardium [31].

LATE GADOLINIUM ENHANCED CARDIAC MAGNETIC RESONANCE (LGE-CMR)

Once necrosis has occurred, myocardial cell contents leak into the interstitium, and the extracellular space alteration induces an inflammatory response. Loss of cardiomyocytes due to AMI leaves an expanded extracellular space where an intravenously administered contrast could accumulate [25].

Magnetic resonance imaging with gadolinium allows reliable assessment of the extent of nonviable and viable myocardium after myocardial infarction. After gadolinium-based contrast agents (GBCAs) bolus administration extravasation into the interstitial (extracellular-extravascular) space (including myocardium) occurs, due to damage of cell membranes. Differences in GBCA concentrations between normal

(viable) and infarcted (nonviable) myocardium are indicative of the extent of infarction [32, 33].

The method allows:

- transmural differentiation of viable versus nonviable myocardium;
- prediction of functional recovery after revascularization in obstructive coronary artery disease;
- prediction of potential complications after myocardial infarction [34].

Echocardiographic estimation of LV-end-diastolic wall thickness < 6 mm was initially reported to practically exclude relevant amount of viable myocardium [35], but additional assessment with LGE-CMR showing no evidence of LGE was later associated with LV function improvement after revascularization with reversal of wall thinning [36].

LGE-CMR provides (indirect) evidence of the existence of even sub-optimally functioning living cardiomyocytes, but the method is still confined mainly to the morphologic characteristics of the myocardium.

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) BASED METHODOLOGIES

The first radioisotope in use was thallium-201 (^{201}Tl) – a potassium alternative. In contrast to nonviable myocardial tissue in viable, Na^+/K^+-ATPase actively transports ^{201}Tl across the myocardial cell membrane. Such intact cell membrane associated transport mechanism contributes to the radioisotope early and delayed redistribution. Several ^{201}Tl viability protocols have been developed for estimation of redistribution – immediately after injection, 4 hours, and even 18-24 hours later [25,37]. ^{201}Tl extraction is proportional to perfusion thus reflecting myocardial perfusion and perfusion defects respectively. However, large radiation doses (up to 30 mSv) and rather poor image resolution led to the search for additional isotopes. Several decades later, ^{201}Tl's substitution by 99mTc-based radiopharmaceuticals was justified by the improved dosimetry, better spatial imaging resolution, leading to greater test accuracy, and less soft-tissue attenuation [38, 39]. ^{99m}Hexakis-2-methoxy-2-methylpropyl-isonitrile (^{99m}Tc-sestamibi, ^{99m}Tc-MIBI) is a lipophilic cationic compound, whose diffusion across the cell membrane is a passive process, but its uptake and retention require functioning mitochondrial and sarcolemma membranes, thus reflecting tissue viability. Such a process excludes the possibility for redistribution and later imaging [40]. Both ^{201}Tl and ^{99m}Tc-MIBI are considered class I agents with similar accuracy for detecting viability [41], and abundant data support prognostic relevance of SPECT in evaluation of the annual risks of cardiac death and myocardial infarction in IHD patients [42, 43, 44]. ^{99m}Tc-nitrido complexes (DBODC5) and mitochondrial complex-1 inhibitors (123I-CMICE-013) are currently being investigated as possible new isotopes, both demonstrating excellent target-to-background ratios [45].

POSITRON EMISSION TOMOGRAPHY (PET)

This method allows evaluation of both myocardial perfusion and viability.

Three PET-tracers are clinically available for perfusion imaging: ^{13}N-NH_3, ^{82}Rb and ^{15}O-H_2O [46]. Estimation of normal perfusion represents an indirect indicator for viability. Instead, in areas with ischemia, additional evaluation of metabolism is useful in order to specify viability of affected tissues. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is a glucose analogue acting as a PET-tracer. Glucose is the primary source of energy – in the healthy heart a shift from fatty acids to glucose is demonstrated during stress, and both acutely and chronically ischemic hearts show preference for Glc over FFAs (as already discussed above). ^{18}F-FDG-PET detects this metabolic shift by demonstrating increased tracer uptake in the viable tissue. Additional PET metabolic tracers that may help in the assessment of myocardial metabolism and its relation to viability include ^{11}C-palmitate (assesses fatty acid metabolism), and ^{11}C-acetate (may be used to quantify myocardial oxygen consumption) [47].

REVASCULARIZATION VS. PHARMACOTHERAPY

IHD is the most common and potentially lethal cause of heart failure [48]. LV dysfunction remains one of the best prognostic determinants of survival in IHD patients [49]. In the same time, the dysfunction of the hypoperfused myocardium is reversible by surgical revascularization – CABG. The most logic first step seems to improve blood flow, and then to switch to medical therapy. Proper assessment of myocardial viability in identifying patients with ischemic cardiomyopathy who might benefit from surgical revascularization justifies the search for new methods for this assessment type. Meanwhile the ultimate benefit of CABG remains controversial.

The Surgical Treatment for Ischemic Heart Failure (STICH) was a multicenter prospective, randomized, open-label trial, sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. 1212 patients with coronary artery disease showing left ventricular ejection fraction of 35% or less were enrolled from 2002 to 2007, with an addi-

tionally extended follow-up period of 5 years [50]. Myocardial viability assessment was originally included as mandatory part of the STICH protocol, yet difficulties in patient enrollment led to subsequent revision – and the decision whether to perform the test was left to the recruiting investigators. Only a subgroup of patients then underwent the viability testing, performed by SPECT and/or dobutamine echocardiography. In that last subgroup, patients with both viable and non-viable myocardium were additionally subdivided in a group undergoing CABG plus pharmacotherapy or a group with pharmacotherapy alone [51].

Initially, results showed an improved long-term all-cause and cardiovascular mortality in patients with surgical revascularization compared with those on medical therapy alone. However, this long-term survival did not take in consideration the short-term (30-day-) mortality after CABG [25]. Moreover, the interaction between the presence or absence of myocardial viability and the beneficial effect of CABG plus medical therapy over medical therapy alone was not significant [52].

Therefore, the question of CABG plus pharmacotherapy or medical therapy alone remains open.

CONCLUSION

Establishment of myocardial viability is an important decision-making factor in the treatment protocol for IHD patients, but it should be in no way the main factor in selecting the best therapy for these patients.

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