Searching for myocardial viability: what method should we choose in patients with severe ventricular dysfunction?

En búsqueda de la viabilidad miocárdica: que metodo elegir en pacientes con deterioro ventricular severo

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ABSTRACT

One of the main causes of left ventricular dysfunction is coronary artery disease. A transient ischemic event generates an imbalance between oxygen supply and demand with reversible damage to myocardial tissue. If persistent in time, this eventevolves from progressive ventricular dysfunction into heart failure. The management of this condition is based on the optimal medical therapy including drugs and, in some cases, combined with myocardial revascularization as an option to improve both quality and quantity of life.

The correct identification of a viable myocardium is essential to know what treatment strategy should be followed. The cardiac magnetic resonance imaging is considered the best imaging modality for the study of myocardial viability, its size, function, valves, and even the aorta. The positron emission tomography imaging modality is also a viable option for a complete study of myocardial viability. Revascularization in patients with severe ventricular dysfunction and myocardial viability reduces mortality, cardiovascular mortality, and hospital stays.

Keywords: *heart failure, myocardial viability, severe left ventricular dysfunction, coronary revascularization.*

RESUMEN

Una de las principales causas del deterioro de la función ventricular izquierda es la enfermedad coronaria. Un evento isquémico transitorio genera un desequilibrio entre el aporte y la demanda de oxígeno, con daño reversible del tejido miocárdico. Si dicho evento persiste, evoluciona con deterioro de la función ventricular de carácter progresivo hasta insuficiencia cardíaca. El tratamiento se basa en una terapéutica médica óptima que incluye fármacos y puede en algunos casos combinarse con la revascularización miocárdica como opción para mejorar calidad y cantidad de vida.

La correcta identificación del miocardio viable es fundamental para una estrategia de tratamiento. Se considera la resonancia nuclear magnética cardíaca como el mejor método para evaluar viabilidad miocárdica, tamaño, función, válvulas e inclusive la aorta. Las imágenes por tomografía por emisión de positrones también presentan una opción para la evaluación completa de la viabilidad miocárdica. La revascularización en pacientes con deterioro severo de la función ventricular y con miocardio viable disminuye mortalidad, mortalidad cardiovascular y reducción de hospitalizaciones.

Palabras clave: *insuficiencia cardíaca, viabilidad miocárdica, deterioro ventricular severo, revascularización coronaria.*

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INTRODUCTION

Heart failure (HF) is a highly prevalent syndrome with high rates of hospitalization, disability, and mortality, and generates costs for the healthcare system. In the presence of mild HF-like symptoms, the annual risk of death is between 5% and 10%. However, it goes up to 30%-40% with severe symptoms and advanced stages of the disease[1].

One of the main causes of left ventricular dysfunction is coronary artery disease. A transient ischemic event generates an imbalance between oxygen supply and demand with reversible damage to myocardial tissue[12]. If persistent in time, this event evolves into progressive ventricular dysfunction. Prolonged ischemia causes the rupture of cellular membranes and myocardial necrosis. The myocardium has mechanisms of acute and chronic adaptation to manage the transient or maintained reduction of coronary blood flow. Thanks to these mechanismsstore enough energy to protect plasma membrane integrity and mitochondrial function at the expense of a lower force of contraction. This complex mechanism of adaptation has been described as hibernating myocardium.

The management of this HF is based on the optimal medical therapy (OMT) including drugs and angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, sacubitril, and aldosterone antagonists. Also, myocardial revascularization combined with these drugs is another option to improve the patients' quantity and quality of life. The treatment strategy is based on the patient's clinical progression and functional state, degree of HF, spread of coronary artery disease, and identification of viable myocardium. The idea we have today of myocardial dysfunction due to transient ischemia is a viable myocardium that exhibits prolonged left ventricular dysfunction after the resolution of a discrete and transient episode of ischemia without evidence of necrosis. The revascularization of ischemic territories offers the possibility of improving the left ventricular (LV) function and, therefore, survival, although it is associated with a non-negligible mortality and morbidity rate.1Therefore, the correct identification of this pathophysiological process and the right selection of patients who may benefit the most is of paramount importance[19]. A high-quality diagnostic methodology is essential here to be able to rule out the presence of hibernating myocardium, determine if the patient should be revascularized or not, receive a heart transplant or remain on medical therapy only.

The objective of this review was to assess the actual evidence on the pathophysiological processes of myocardial metabolism in the presence of ischemia and the adaptative

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responses of myocardial tissue, the role of detecting viability in patients with severe ventricular dysfunction, the different diagnostic methods available today to assess myocardial viability, the indicators, and the results of revascularization in selected patients.

MATERIALS AND METHODS

An intense search of the different bibliographic sources was conducted between 2000 and 2019.

Randomized clinical trials, reviews, original articles, and medical consensus papers were looked into. The browser most often used for the searches was PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) that gives free open access to MEDLINE bibliographic database that includes references and abstracts on biomedical researchand is run by the United States National Library of Medicine.

Also, non-indexed searches on consensus papers by the Argentine Society of Cardiology (SAC) were conducted since the knowledge accumulated in our field was considered necessary as well.

The following keywords were used in our queries both in isolation or combined with each other: "myocardial viability", "severe left ventricular dysfunction", "low ejection fraction", "myocardial stunning", "myocardial hibernation", "chronic heart failure","ischemia", "revascularization", " PCI", "MRS."

When we had all the bibliographic material available, we proceeded to classify it by date and relevance. Articles published both in scientific journals with the highest impact factor and in Spanish or English were included. Low-impact journals or with a low number of patients recruited (such as brief communications and case reports) and papers published in languages different from the aforementioned were excluded.

DEFINITIONS

Ischemic heart disease is defined as a myocardial dysfunction due to occlusive or obstructive coronary artery disease[4].

There are different pathophysiological processes involved in Ischemic heart disease: stunned myocardium, hibernating myocardium or cellular death, and myocardial necrosis. Myocardial viability is defined as a tissue with enough blood flow to be able to preserve the integrity of cellular membranes and preserve metabolic activity with reversible dysfunction of the force of contraction.

Severe left ventricular dysfunction is defined as a left ventricular ejection fraction ≤35%. The complete optimal medical therapy (OMT) is theone recommended by clinical practice guidelines: diuretics, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II-receptor antagonists (ARAII) or angiotensin receptor-neprilysin inhibitors (ARNI), aldosterone antagonists (AA), and beta-blockers (BB) for the management of patients with severe ventricular dysfunction.

PATHOPHYSIOLOGY: MYOCARDIAL CELLULAR METABOLISM

The main function of cardiac muscle cells (cardiomyocytes) is to perform the cardiac cycle of contraction and relaxation. Under baseline conditions energy-rich sulfates like adenosine triphosphate (ATP) provide the energy needed togenerate the contraction of cardiomyocytes. The ATP is produced through 2 different metabolic processes called oxidative phosphorylation and glycolysis[5]. When oxygen supply is normal, the metabolism of free fatty acids generates ATP and citrates that accumulate in the myocardial tissue suppressing the oxidation of glucose.

In the presence of sudden drops of coronary blood flow, the cardiac muscle starts producing energy from the anaerobic metabolism of glucose. This causes contractility disorders, a reduced action potential of the membranes, and changes in the conduction system. The production of high-energy phosphates through anaerobic glycolysis leads to the accumulation of glucose-1-phosphate, glucose-6-phosphate, α-glycerophosphate, and lactate. As a result of this process, intracellular pH drops causing the accumulation of osmotically activeparticles (construct of glycolytic pathway) causing intracellular edema. The increased concentration of intracellular hydrogen ion (H^+) induces the entry of sodium through the Na^+/H^+ exchange. In turn, an excess of sodium induces the entry of calcium through the Na^+/Ca^{++} exchanger[6]. Calcium overload can change troponin levels contributing to a sensitivity loss to myofibrils inducing myocardial contractility alterations. In states of severe hypoperfusion, the rephosphorylation of ADP to ATP (draining the reserves of high-energy phosphates) and glyclolytic enzymes are inhibited rupturing the cellular membrane and inducing cellular death.

Before cellular death arrives, the myocardium develops mechanisms of acute and chronic adaptation to the transient or maintained reduction of coronary blood flow: stunned myocardium and hibernating myocardium. Within the clinical setting both adaptative responses may coexist.

Stunned myocardium is due to the sudden reduction of coronary flow, which induces transient severe ischemia and reversible ventricular dysfunction if myocardial tissue perfusion can be recovered (depressed function at rest, preserved perfusion). Myocardial contractility often recovers within 1 to 2 weeks[7].

Hibernating myocardium can be associated with reduced chronic contractility due to prolonged hypoperfusion at rest (reduced function and perfusion at rest) or to transient reduced coronary blood flow (repetitive stunning). Some studies have confirmed that tumor necrosis factor alpha (TNF-α) and nitric oxide are overexpressed here promoting fibrosis and lack of myocardial contractile reserve[8,9].

Unlike stunned myocardium, at histological level, hibernating myocardium presents changes both at the intra and extracellular levels. There are more glycogen deposits, loss of serial sarcomeres, myofibrils, and extracellular fibrosis. The severity of extracellular changes is associated with contractility recovery time after flow restoration.

Hibernating myocardium is a process of persistent exposure to coronary hypoflow with diffuse epicardial compromise that progresses to local and globalventricular systolic dysfunction. After revascularization, the hypokinetic myocardium can delay the recovery of contractile function between 6 to 12 months[3]. The reversibility of ventricular dysfunction will depend on the presence of viable myocardium. Therefore, if blood flow is restored, both the

stunned and the hibernating myocardia are potentially recoverable tissues.

For all these reasons, the prerequisites of cellular viability are:

1. the presenceof enough myocardial blood flow to carry substrates to cardiac myocytes for metabolic processes and eliminate final products of metabolism;
2. the integrity of the cellular membrane; and
3. the preservation of intracellular metabolic activity.

We should mention how important it is to establish the presence of myocardial viability in patients with severe ventricular dysfunction because it is still possible to optimize treatment and restore the perfusion of myocardial tissue.

VIABILITY ASSESSMENT. DIAGNOSTIC METHODS

In patients with HF, it is necessary to determine whether cardiac myocyte scan restore their contractile function if perfused properly. There are different diagnostic methods available to confirm the presence of viable myocardium:

1. Dobutamine stress echocardiography;
2. Single-photon emission computed tomography (SPECT);
3. Positron emission tomography (PET);
4. Cardiac magnetic resonance imaging (CMR).

Dobutamine stress echocardiography

Stress echocardiography is an excellent imaging modality to assess and compare contractile reserve by measuring its motility, size, shape, and parietal thickness. Contractile reserve is the capacity of a myocardial segment to increase its performance after stimulation. The detection of contractile reserve with low doses of dobutamine is the distinctive seal of a viable myocardium.

The normal LV response to an increased workload represents a uniform increase of parietal motility, regional thickness, and a reduction of size of the end-systolic left ventricular cavity with minimum changes of diastolic size during exercise in vasodilatation. The motion and thickness of the wall during systole can be normal, reduced (hypokinetic), abnormal (dyskinetic) or absent (akinetic) in the dysfunctional left ventricle due to ischemia[10]. A reduced thickness of diastolic wall in the dysfunctional LV is indicative of scar tissue while a hypokinetic or dyskinetic segment with preserved systolic wall is probably indicative of a viable myocardium. A ≥6 mm myocardial thickening at the end of the diastole is considered viable while a thin, echogenic segment (fibrotic) is suggestive of scar.

The administration of dobutamine induces the contractility of viable segments both stunned and hibernating. The dobutamine-sensitive improved parietal motion predicts the later improvement of the regional thickening of the LV wall after revascularization[5].

In the early phase, doses of 5-10 μg/kg/min of dobutamine are used. Doses of up to 10-40 μg/kg/min can be administered to detect ischemia. The viable myocardium has a biphasic pattern of response to dobutamine. During infusion at low doses, an improved parietal motion of the dysfunctional myocardium can be seen due to coronary flow and the recruitment of myocardial contractile reserve. With higher doses, coronary flow will be reaching its limit. However, it will never go over the limitdue to ischemia and the presence of coronary artery stenosis irrigating the region. A worse parietal motility will be seen too. The sensitivity and specificity of predicting the recovery of myocardial function using dobutamine stress echocardiography is 71% to 97% and 63% to 95% respectively, which is associated with a biphasic pattern of response that increases the degree of prediction.

This method has limitations regarding qualitative assessment with high interobserver variability and presence of poor acoustic window in some patients to be able to conduct the study.

We have the possibility of administering IV contrast that causes microbubbles that behave quite like red blood cells (due to their molecular weight) and cause myocardial opacification, which is indicative of the integrity of vascular microcirculation. In a viable myocardium there is normal or irregular segment perfusion. However, in a non-viable myocardium there is no perfusion. Contrast echocardiography can distinguish a stunned myocardium from necrosis. This imaging modality has higher sensitivity and similar specificity compared to dobutamine stress echocardiography.

Single-photon emission computed tomography (SPECT)

It is a nuclear cardiology imaging modality where injected radiotracers are captured by the viable myocardium. The cardiomyocytes extract the isotope from the blood retaining it over a certain period of time. The myocardium emits photons based on the number of radiotracers captured which is associated with the perfusion of myocardial tissue. A gamma camera is used to capture these gamma-ray photons and turn them into visible light data. The final result of the SPECT is the creation of multiple slices that make up a digital image that represents the distribution of radiotracers in the heart. The 3D reconstruction is performed with images from the LV 3 myocardial axes: short axis, horizontal long axis, and vertical long axis.

The radiotracers used to perform a SPECT are thallium 201 and 3 classes of markers with technetium-99m: sestamibi, tetrafosmin, and teboroxim[17]. Thallium 201 is a monovalent cation with biological properties similar to potassium. It is captured by cardiomyocytes with integrity of their membranes through the Na^+/K^+/ATPase pump (active transport) and facilitated diffusion (approximately 85% of radiotracers). The maximum concentration of thallium occurs within the first 5 minutes depending on blood flow. Redistribution starts between 10 to 15 minutes after the injection of the tracers and depends on the intensity of the myocardial excretion of thallium. The kinetics of secretion is faster in normal myocardial tissues and slower in ischemic myocardia.

The uptake defect reversal since the initial overload until the acquisition of redistribution images (between 3 and 4 hours later) is indicative of viable myocardium with reversible ischemia. In the administration of thallium at rest, the reversibility of the initial uptake defect after late redistribution is indicative of viable myocardium with hypoperfusion at rest. The viable tissue can be identified when the late images show significant filling of the defects found on the early studies (absorption increase >10%) or in the pres-

ence of defect reversal while marker activity is >50%[15]. On the other hand, necrotic myocardium shows an uptake defect both at rest and in redistribution images (a steady-state defect).

In some patients, uptake can be very much reduced after overload and not show the redistribution of images after 3 to 4 hours—even 24 hours later—due to coronary artery disease and presence of highly ischemic regions. The viable myocardium can be regulated by increasing the concentrations of thallium in blood through the reinjection of small doses at rest.

Sestamibi is the most studied liposoluble cationic compound 10 and the most widely used of these agents. The dispersion of Tc 99m in the myocardium is proportional to blood flow mainly through passive diffusion and gets trapped inside the mitochondria by the membrane electrochemical gradient. The absorption of these radioactive substances requires viable myocardial cells and an intact cellular membrane[10]. The studies conducted with Tc 99m require 2 separate injections: during maximum overload and at rest. That is how the reversibility of the uptake defect will present in the presence of viable myocardium, although it will not possible to distinguish a stunned from a hibernating myocardium. Tc 99-based tracers have a shorter half-life and exposure to radiation, and a greater preponderance of high-energy gamma emissions that reduce soft-tissue attenuation compared to thallium 201. The addition of nitrates improves both the uptake of the tracers and the accuracy of this imaging modality. Different studies were conducted comparing SPECT and PET (positron emission tomography) and SPECT underestimated the presence of myocardial viability. One of the setbacks of this imaging modality is its non-uniform soft-tissue attenuation (breast tissue, diaphragm or other extracardiac structures close to the heart) that degrades the quality of the images acquired or creates artifacts that mimic the actual anomalies of perfusion. Attenuation correction can improve the accuracy of viability tests using SPECT techniques. Attenuation correction should be patient-specific with an attenuation map created for image acquisition purposes.

Positron emission tomography (PET)

This imaging modality uses nuclear technology to detect segments with reduced perfusion and/or myocardial metabolism in quantitative terms (which is an advance over the SPECT)[20]. Two different categories of positron-emitting radiotracers are used: 1) perfusion: rubidium-82 and [13N] ammonia; 2) metabolic tracers: [18F] fluoro-2-deoxy-D-glucose (FDG). The study protocol includes 2 parts: the initial study of myocardial perfusion and the study of myocardial metabolism. Traditionally, a study at rest is conducted that can also be used to study exertional ischemia if necessary.

Diagnoses are achieved by comparing the distribution of radiation activity to normal parameters or by measuring the rate of accumulation or disappearance of radioactivity in the long-term[18]. In normal conditions, the myocardium uses the oxidation of free fatty acids as energy source. However, in the presence of coronary flow alterations (presence of ischemia), oxidative metabolism is reduced, and the anaerobic metabolism of glucose is activated. The FDG uses the same transporter as glucose to enter the cell which is why the FDG uptake is a marker of the glucose metabolism present in the viable myocardium. Four different uptake patterns during image acquisition can be distinguished: 1) mismatch between perfusion and metabolism: there is a reduced myocardial perfusion and contractile function with a normal FDG uptake suggestive of the presence of viable myocardium: hibernating; 2) regions of perfusion and normal metabolism with motility dysfunction in segments: it can be representative of a stunned myocardium and, in conditions of ventricular dilatation of the presence of remodeling; 3) segments with reduced perfusion and metabolism indicative of the presence of necrotic effects; and 4) reverse mismatch: normal perfusion with a reduced FDG uptake as seen in early revascularization after infarction, right branch bundle block, non-ischemic heart disease, and diabetes mellitus[13].

Myocardial blood flow is a marker of viability because the viable tissue requires blood supply. Blood flow is often within normal or almost normal ranges in dysfunctional though viable myocardium suggestive that most of the reversible dysfunction is indicative of repetitive stunning, not hibernation. As described before, PET myocardial perfusion quantification is often used with the PET metabolic findings to identifyviable myocardium that may benefit from revascularization.

Cardiac magnetic resonance imaging (CMR)

CMR is a noninvasive imaging modality that does not use radiation. Instead, it uses a powerful magnetic field, radiofrequency impulses, and a computer to generate detailed images for the assessment ofmyocardial viability. Also, it provides information on the anatomy, global and regional left ventricular function, ischemia, and coronary flow. The phenomenon of magnetic resonance imaging occurs in the hydrogen nuclei (abundant in the human body and highly sensitive) that behave like magnets aligned with an external magnetic field. The excitement and relaxation of these nuclei transmits as a signal that can be used to generate images. Contrast among different tissues in the images depend on excitement delay, signal reading (TE or echo time), and the time elapsed between repeated excitements and radio waves (TR or repetition time). The different ways of contrast derive from 2 processes of main relaxation that affect net magnetization: the decay in the longitudinal axis (T1) and in the cross-sectional view (T2). The CMR draws a spatial map of radio signals[5].

Two types of cardiac magnetic resonance imaging are often used to assess myocardial viability: dobutamine stress cardiac magnetic resonance imaging (DS-CMR) for the assessment of motility and parietal thickening, and delayed contrast-enhanced cardiac magnetic resonance imaging (CE-CMR) to distinguish ischemic from non-ischemic cardiomyopathies and be able to assess the presence of myocardial damage due to necrosis, fibrosis, inflammation or infiltration.

Dobutamine stress cardiac magnetic resonance imaging

As it occurs with the echocardiography, it is used to measure the left ventricular dysfunction contractile reserve. The administration of dobutamine shows areas with contractile dysfunction and preserved parietal thickness (>5 mm) indicative of preserved viability. The presence of transmural scar tissue between 50% and 75% of parietal

thickness is suggestive of a myocardial tissue that will not improve after revascularization. The improved contractile reserve seen after the administration of dobutamine, the parietal thickness seen at the end of diastole, and the quantification of necrotic tissue predict benefits for the myocardium if revascularized.

Gadolinium-based magnetic resonance imaging (late enhancement).

Several contrast agents can be used although for the management of cardiovascular system substances with gadolinium are used. This contrast agent is administered intravenously and remains at extracellular level. Therefore, under normal conditions, contrast never enters the cell. However, in the infarction or chronic fibrosis setting, the extracellular compartment expands at the expense of cellular disruption and the distribution of contrast is different. The kinetics of how gadolinium enters the myocardial infarction (MI) territory is delayed and after 10 to 15 minutes the distribution of gadolinium can be perfectly seen. The regions of necrotic tissue will show a high concentration of contrast (bright) compared to normal myocardium (black). Several patterns with gadolinium have been described: in the MI setting, there is late enhancement at subendocardial level with transmural spread depending on the size of infarction. Conversely, the presence of subepicardial late enhancement and at mid-wall level—whether diffused or in a patchy pattern—rules out the possibility of ischemic compromise. The spread of transmural enhancement is opposite to the prediction of functional recovery with revascularization, meaning that the presence of transmural late enhancement >50% of the wall has fewer chances of improving with treatment.

In the clinical practice, the visual estimate is the easiest method to quantity late enhancement with gadolinium by establishing a percentage of the infarcted myocardial thickness in relation to the global wall to be able to define transmural spread. A model established by the American Heart Association (AHA) is used. This model divides the ventricle into 17 segments with scores tha go from 0 to 4 (0: no scar; 4:100% scar tissue). The segments final score divided by the total number of segments allows accurate assessments of the compromised ventricular mass[7].

Late CMR imaging with gadolinium detects Q-wave MI and non-Q-wave MI accurately with such high sensitivity that it can show small MIs that cannot be seen on the SPECT[5]. Former studies have proven that the CMR can distinguish between the infarct core and the adjacent peri-infarction area that appears with a lower signal intensity due to the mixture of infarction and viable tissue. The larger the peri-infarction area the higher the chances of cardiac death and cardiovascular events in the future[16].

T1-mapping allows global and regional analyses of myocardial structure at microscopic level. Signal intensity at T1-weighed imaging is altered due to an increase of water or fibrosis in the tissue. The signal intensity at T1-weighed imaging intensifies in the presence of edema due to myocardial lesion, cellular edema, and necrosis and in cases of diffusion of extracellular space due to amyloidosis or focal or diffuse fibrosis[7].

The advantages of CMR include the capacity to provide simultaneous information on anatomy, function, and perfusion with high-quality images.

DISCUSSION

The detection of viable myocardium is essential to determine the optimal therapy of a subgroup of patients with HF due to atherosclerotic coronary artery disease.

Over the last few years several studies have been conducted on the recovery of cardiac contractility after revascularization in subjects with severely depressed ventricular function. These studies suggest that, currently, the CMR is the best option available to determine cardiac viability. However, since it is an expensive imaging modality that is not fully available everywhere, in our setting the remaining imaging modalities are valid options for the detection of viable myocardium.

The STICH trial[2] is a randomized, multicenter study with 2 study hypotheses. The so-called Hypothesis #1 suggests that myocardial revascularization surgery (MRS) plus the optimal medical therapy (OMT) may reduce mortality compared to only the optimal medical therapy. From 2002 to 2007, a total of 1212 patients recruited were identified using SPECT or dobutamine stress echocardiography for the detection of myocardial viability and to assess all-cause mortality as the primary endpoint. The study secondary endpoints were cardiac death and hospitalizations. This study compared 602 patients who received OMT to 610 patients who received OMT plus conventional MRS. Nearly 17% of the patients from the OMT group were finally treated with revascularization therapy. Reasons were symptom progression (40%), acute decompensation (27%), family decision (28%), and the doctors' best clinical judgement since the study was not double-blind (5%). The median follow-up was 56 months until 2010. All-cause mortality rate (primary endpoint) was 41% in those who received OMT and 36% in those treated with MRS (hazard ratio of MRS=0.86, 95%CI [0.72-1.04], P =.12) **(Figure 1)**. The cardiovascular mortality rate was 33% and 28% in patients treated with OMTand MRS, respectively (hazard ratio MRS=0.81, 95%CI [0.66-1], P =.05). Sixty-eight-percent of patients treated with OMT and 58% of patients treated with MRS were hospitalized due to cardiovascu-

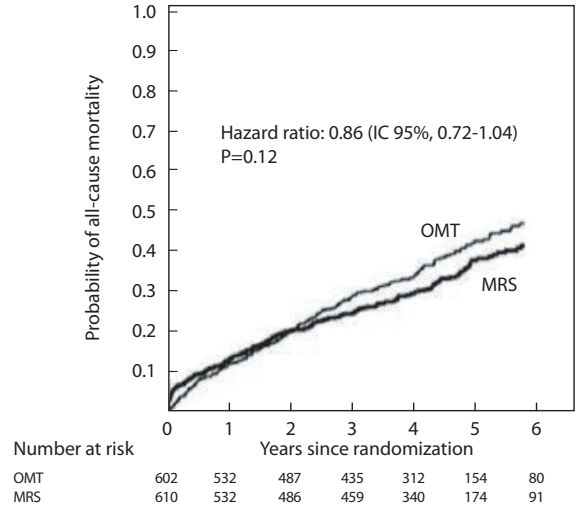

Figura 1. *Adapted from Velazquez EJ et al. Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction. New England Journal of Medicine (2011). .*

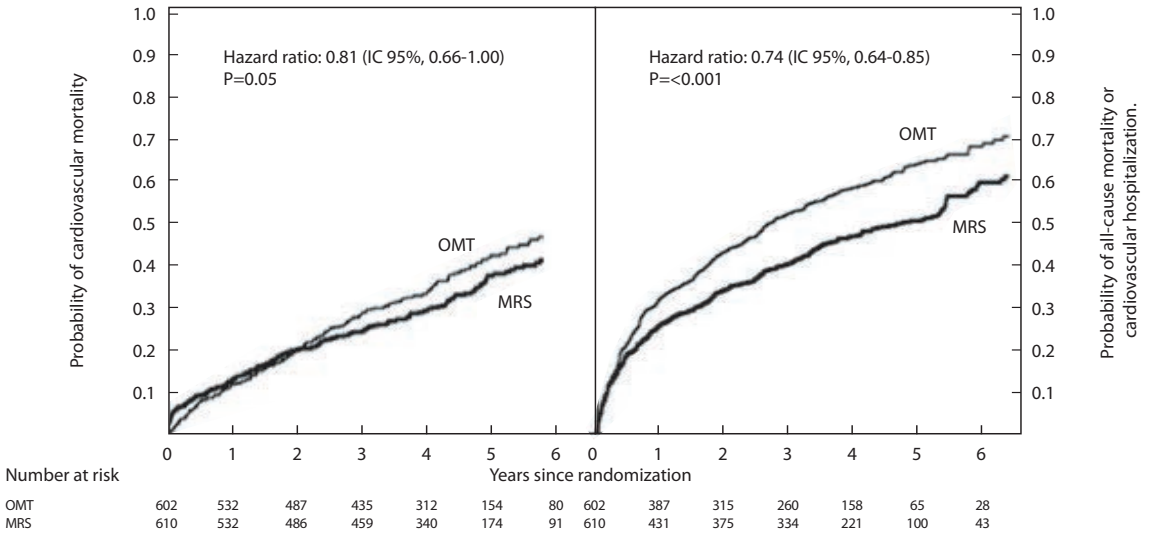

Figure 2. *Adapted from Velazquez EJ et al. Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction. New England Journal of Medicine (2011). The Kaplan-Meier curves of the STICH trial show a statistically significant benefit over OMT on the probabilities of cardiovascular mortality, all-cause mortality or cardiovascular hospitalization.*

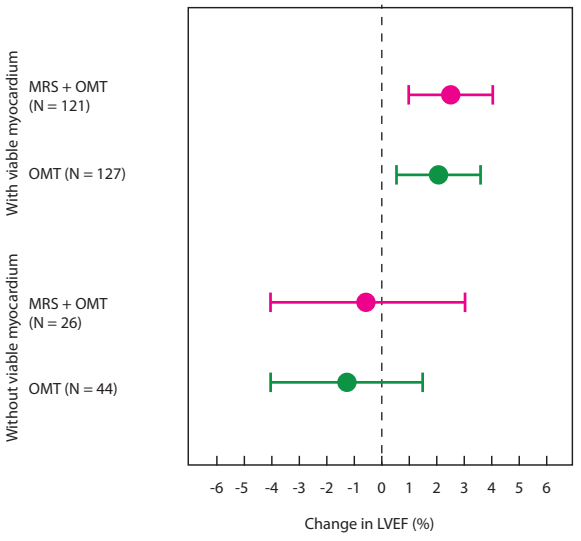

Figure 3. *Adapted from Panza JA et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy, New England Journal of Medicine (2019). Left ventricular ejection fraction improved in patients with myocardial viability. Those who benefited the most were revascularized patients..*

lar causes (hazard ratio of MRS=0.74, 95%CI [0.64-0.85], P <.001) (**Figure 2**). The intention-to-treat analysis showed a significant difference between both groups regarding the all-cause mortality rate. However, it was significantly favorable to patients treated with MRS regarding mortality and hospitalizations due to cardiovascular causes. However, the STICH trial was severely criticized[11]. In the first place, the detection of viability was determined by the doctors involved in the study based on availability with not much use of CMR, considered the best diagnostic imaging modality, or PET that also has high rates of sensitivity and specificity to assess myocardial viability. In the second place, this was not a double-blind study, meaning that the clinical knowledge of the patients by the doctors may have impacted the reasons that eventually led to hospitalization. Finally, no significant benefit was seen after years of follow-up.

In 2016 the STICHES trial was published[14]. The 10-year results showed a significant reduction of the main variable of all-cause mortality in patients randomized to MRS. This long-term follow-up study establishes that patients with ischemic heart disease and left ventricular dysfunction benefit from revascularization. In the presence of dilated ischemic-necrotic cardiomyopathy with evidence of myocardial viability, MRS seems beneficial as long as the conditions established in the STICH trial are observed (surgical centers experienced in the management of patients with moderate-to-severe ejection fraction dysfunction and low mortality rate). For the management of severe ventricular function dysfunction with a significantly viable myocardial mass (>20%), MRS seems like a good and valid treatment option if the coronary anatomy is technically eligible for bypass surgery.

Back in 2019, a subanalysis of the STICHES trial[23] was published. It assessed the correlation between the detection of myocardial viability and the benefit of revascularization and medical therapy. However, it did not provide enough statistical evidence on the presence of myocardial viability and lower mortality rate. However, the ejection fraction actually improved in patients with viable myocardium regardless of the treatment used (**Figure 3**). The authors mention the existence of a biological correlation between myocardial viability and the benefit of revascularization that could not be proven maybe because of the number of patients with non-viable myocardium (19%) compared to those with actually viable myocardial (81%).

The clinical guidelines of the European Society of Cardiology (ESC)[21] establish the benefit of revascularizing patients with ischemic-necrotic chronic HF and severe ventricular dysfunction. This benefit may be actually seen in practice by performing a baseline CMR and after revascularization resulting in improved ejection fraction and regional motility (**Figure 4**). Although clinical practice guidelines recommend revascularizing these patients, the optimal strategy has not been established yet. Both MRS

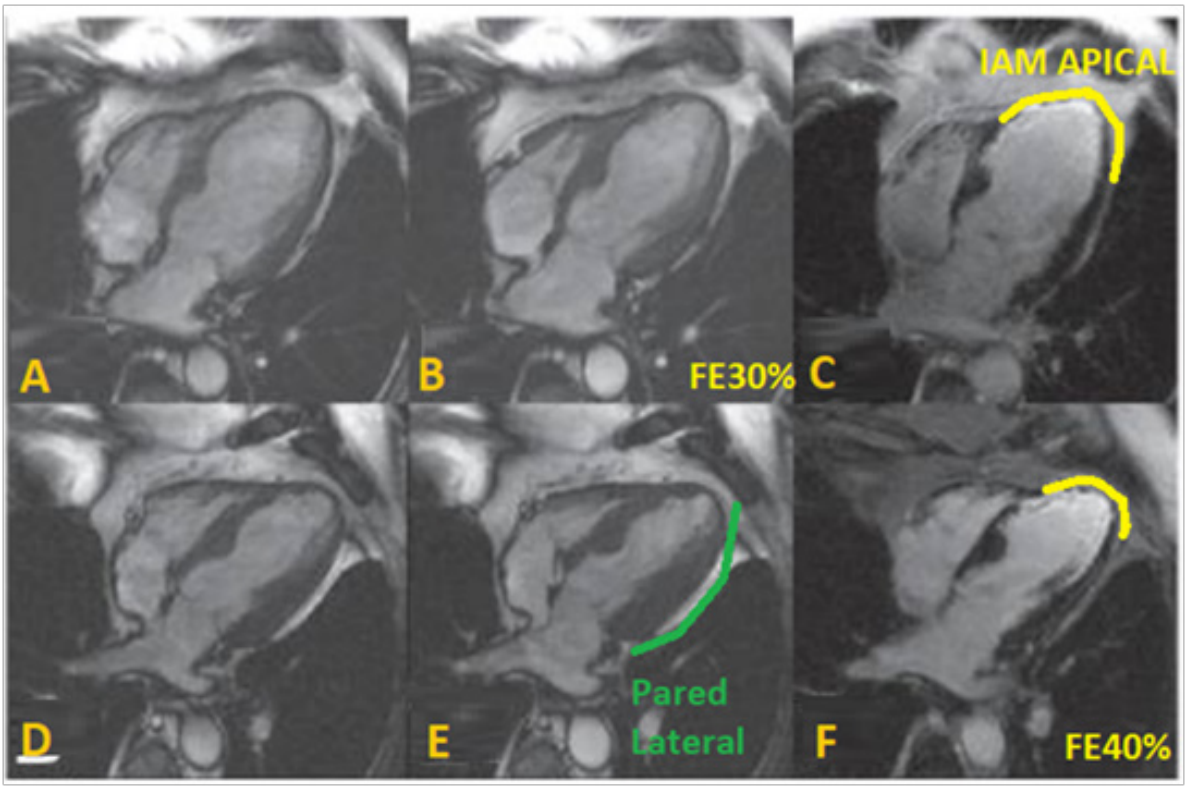

Figura 4. *Adapted from Thielmann M et al. Magnetic resonance imaging in coronary artery bypass surgery – improvement of global and segmental function in patients with severely compromised left ventricular function by M Thielmann. Vasc Health Risk Manag (2007). Cardiac magnetic resonance imaging of a 64-year-old male patient before (upper line) and after (lower line) coronary revascularization. The end-diastolic (A) andend-systolic images (B) reveal a severe left ventricular systolic dysfunction before surgery (EF of 30%) that is akinetic in the inferior septal wall, apical anterolateral wall,and apical wall, and hypocineticin the lateral basal and mid wall. The image in (C) shows wide late subendocardial enhancement (bright signal) in the apical septum, thin in the lateral wall, and transmural in the apex indicative of chronic scar. The left ventricular function after surgery (D, E) does not show an improved apical septum or apex while the entire lateral wall actually improved and turned normokinetic. No changes were seen on the spread of the scar (F). The global left ventricular function improved with an EF of 40% while left ventricular volumes decreased.*

and percutaneous coronary intervention (PCI) should be assessed and decided upon by the heart team while taking into consideration the patient's opinion, his coronary anatomy, comorbidities, and myocardial viability. The clinical trials that compared MRS and PCI often exclude patients with ventricular ejection fractions ≤35%.

The clinical practice guidelines (2016) of the Argentine Society of Cardiology (SAC) for the management of chronic heart failure establish that the coronary revascularization of ischemic territories may improve left ventricular function and survival and should be considered in all patients with HF. Therefore, it is of paramount importance to know what patients with myocardial viability may benefit from this intervention. Therefore, the SAC guidelines recommend MRS or PTA (percutaneous transluminal angioplasty) in patients with severely depressed left ventricular ejection fraction and a significant lesion in the left main coronary artery or its equivalent or multiple vessel disease with compromise to the proximal left anterior descending coronary artery with myocardial viability (Class I, level of evidence C). Also, the SAC guidelines recommend MRS in patients with ventricular dysfunction and a significant non-contractile myocardial mass without the coronary characteristics described above (Class IIa, level of evidence B)[1].

At the same time, in its guidelines for the management of ST-segment elevation acute myocardial infarction published in 2015, the SAC recommends assessing myocardial viability (without establishing a specific method including echocardiogram, SPECT, PET or CMR) in patients with multiple vessel disease or in cases where myocardial revascularization may be considered (Class I, level of evidence C)[22].

CONCLUSION

Myocardium develops different adaptative processes to manage transient or chronic ischemia. Both myocardial stunning and myocardial hibernation suggest viability states that can be reversed through revascularization by eliminating exposure to ischemia.

The correct identification of viable myocardium is essential to develop a therapeutic strategy based on OMTand revascularization. The cardiac magnetic resonance imaging is considered the best imaging modality of all due to its high resolution and quality of images regarding myocardial viability. Also, because it provides additional information on thesize and function of the left ventricle and other structures (valves, aorta) that can contribute to the strategy to be followed. However, PET is also a valid option for the complete assessment of myocardial viability compared to the other imaging modalities. Hybrid imaging modalities are still in the pipeline for future use in clinical practice.

Revascularization plus the optimal medical therapy improved mortality, cardiovascular mortality, and shortened the hospital stay. The detection of these myocardial adaptative processes that have been known for decades has not been statistically confirmed yet. In this context, the pres-

ence of myocardial viability should be interpreted individually in each particular case to be able to choose the best possible treatment.

Both the ESC and the SAC inform on the role that the detection of myocardial viability plays in the comprehensive assessment of patients with ischemic-necrotic HF and severe ventricular dysfunction to determine the best therapeutic strategy and what patients will benefit from such strategy.

REFERENCES

1. *Consenso de insuficiencia cardiaca crónica, Sociedad Argentina de Cardiología. Buenos Aires, Argentina. 2016; vol 84, suplemento 3.*
2. *Velazquez EJ, Lee KL, Deja MA, et al. Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction. N Engl J Med 2011;364(17):1607-16.*
3. *Carluccio E, Biagioli P, Alunni G, et al. Effect of revascularizing viable myocardium on left ventricular diastolic function in patients with ischemic cardiomyopathy. Eur Heart J 2009;30(12):1501-9.*
4. *Koslowki P, Cragnolino D, Masoli O. Viabilidad miocárdica: conceptos fisiopatológicos para el diagnóstico y la selección del tratamiento. Revista Argentina de Cardiología 2001;69:427-38.*
5. *Libby, Bonow, Mann, Zipes. Braunwald - Tratado de cardiología (8th ed.), Elsevier Saunders, 2009. Cap. 14, Cap. 16, Cap. 17.*
6. *De la Serna F. Insuficiencia Cardiaca Crónica. Federación Argentina de Cardiología. Buenos Aires, 2011.*
7. *Patel H, Mazur W, Williams K, Kalra D. Myocardial viability–State of the art: Is it still relevant and how to best assess it with imaging? Trends Cardiovasc Med 2018;28(1):24-37.*
8. *Kalra DK, Zhu X, Ramchandani MK, et al. Increased myocardial gene espression of tumor necrosis alpha and nitric oxide synthase-2: a potential mechanism for depressed myocardial function in hibernating myocardium in humans. Circulation 2002;105:1537-40.*
9. *Elsässer A, Decker E, Kostin S, et al. A self-perpetuating vicious cycle of tissue damage in human hibernating myocardium. Moll Cell Biochem 2000;2013:17-8.*
10. *Health Quality Ontario. Positron emission tomography for the assessment of myocardial viability: an evidence-based analysis. Ont Health Technol Assess Ser 2010;10(16):1-80*
11. *Cortigiani L, Bigi R, Sicari R. Is viability still viable after the STICH trial?. Eur Heart J Cardiovasc Imaging 2011;13(3):219-26.*
12. *Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications. Circulation 2001;104:2981-9.*
13. *Anavekar N, Chareonthaitawee P, Narula J, Gersh B. Revascularization in Patients with Severe Left Ventricular Dysfunction. J Am Coll Cardiol 2016;67(24):2874-87.*
14. *Velazquez E, Lee K, Jones R, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. N Engl J Med 2016;374:1511-20.*
15. *Health Quality Ontario. Magnetic Resonance Imaging (MRI) for the Assessment of Myocardial Viability: An Evidence-Based Analysis. Ont Health Technol Assess Ser 2010;10(15):1-45.*
16. *Yan AT, Shayne AJ, Brown KA, et al: Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. Circulation 2006;114:32.*
17. *Di Carli M. Hybrid Imaging: Integration of Nuclear Imaging and Cardiac CT. Cardiol Clin 2009;27(2), 257-263.*
18. *Partington SL, Kwong RY, Dorbala S. Multimodality imaging in the assessment of myocardial viability. Heart Fail Rev 2011;16(4):381-95.*
19. *Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability and prognosis in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2002;39:1159-62.*
20. *Candell-Riera J. Presente y Futuro de la Cardiología Nuclear. ¿De dónde venimos y hacia dónde vamos?, Hospital Universitari Vall d'Hebron. Barcelona, España. Rev Fed Arg Cardiol 2014;43(2):64-70.*
21. *Neumann F, Sousa-Uva M, Ahlsson A, et al. ESC Scientific Document Group; ESC/EACTS Guidelines on myocardial revascularization, Eur Heart J 2018.*
22. *Consenso de Infarto Agudo de Miocardio con elevación del segmento ST. Sociedad Argentina de Cardiología. Buenos Aires, Argentina. 2015.*
23. *Panza JA, Ellis AM, Al-Khalidi HR, et al. Myocardial viability and long term outcomes in ischemic cardiomyopathy. N Engl J Med 2019;381:739-48.*