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Editorial

Microvascular injury after acute myocardial infarction. Focus on the catheterization laboratory

Daño microvascular tras un infarto agudo de miocardio. Foco en el laboratorio de hemodinámica

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Until the early 20th century, acute thrombotic occlusion of a coronary artery was considered a condition associated with practically immediate death.[1] In 1919, James B. Herrick treated this paradigm for the first time and published a small number of cases of patients with acute thrombosis of the coronary arteries, most likely with acute ST-elevation myocardial infarction (STEMI), who survived for a matter of hours or days.[1] The last century and especially the last 60 years have seen one of the most fascinating journeys of modern medicine. The development of the external defibrillator, coronary care units, advances in primary and secondary prevention and, above all, coronary reperfusion therapy (first with fibrinolysis then later the widespread use of primary angioplasty and intracoronary stents) have led to a drastic reduction in the acute mortality of STEMI to levels of around 10%

Over the last 20 years, this trend has slowed and we have seen a levelling off in the falling mortality curve for patients with STEMI. Furthermore, since the introduction of reperfusion with primary angioplasty, the scientific community noted that a considerable number of patients were still having extensive infarcts, potentially leading to heart failure and death. A key point for understanding these observations is that, despite an apparently successful epicardial reperfusion of the culprit artery in the catheterization laboratory, severe microvascular damage can occur to the complex and extensive microvascular network.[2,3]

This phenomenon, described for the first time by Kloner et al. in an animal model[4] and later documented in patients, consists of a state of tissue hypoperfusion despite the epicardial coronary flow being reestablished. Although distal embolization of thrombotic material plays an important role, this is not the only determining factor, nor (probably) the most important. The pathophysiology is multifactorial, but some of the central mechanisms are loss of endothelial integrity (both microvascular and arterial), ischemia-reperfusion damage, vasoconstriction, uncontrolled inflammatory response, and microvascular compression from edema and tissue hemorrhage as a consequence of the increased endothelial permeability.[3]

Cardiac magnetic resonance (CMR) has been fundamental in improving the understanding and detection of microvascular damage after infarction and has made a huge contribution to transforming this concept from a subject of interest in basic research to a relevant factor to be considered in the clinical management of patients with STEMI.[2,3,5] Microvascular damage detected on CMR is known as microvascular obstruction (MVO). As much as 50% of all reperfused STEMI patients and up to 30% of those with angiographic reperfusion of an apparently normal epicardial artery, with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, have MVO, which has deleterious structural and prognostic effects.[2] Recent studies have shown conclusively that the presence of extensive microvascular damage in patients with STEMI treated with coronary revascularization strategies is one of the strongest predictors of adverse remodeling, heart failure, and death.[2,3,5]

Over the past 30 years, the catheterization laboratory has been pivotal in STEMI diagnosis and its treatment with coronary reperfusion. In a recent article published in *Revista Española de Cardiología*, Shin et al. present an interesting study that validated an easy-to-use angiographic method that allows, simply and without prolonging the procedure, the early detection in the catheterization laboratory of microvascular damage following reperfusion.[6] The importance of microvascular (not only epicardial) reperfusion makes it necessary to broaden the focus of attention to its improved diagnosis and reflect on how to pose future therapeutic opportunities that, as adjuvants to coronary reperfusion, would allow better management of this phenomenon.

Regarding diagnosis, there are simple and widely-available methods that suggest the existence of a microvascular reperfusion deficit, as well as noninvasive and invasive imaging techniques, that can confirm and quantify the extent of the damage.[2,3]

Regarding the simple, widely-available methods, some indirect markers such as a higher necrotic enzyme peak and higher increase in leucocytes (especially the neutrophil/lymphocyte ratio) are nondefinitive markers but, as they are tested sequentially and in all

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patients, they represent the first red flag for the diagnosis.[3] New serological markers specific for microvascular damage have recently been described, which may be useful for diagnosis, and above all to advance understanding of the pathophysiology of this phenomenon.[7] However, if suspected, the electrocardiogram is the essential early tool.[3] Specifically, persistent ST-segment elevation after revascularization and even a slight residual ST elevation in the leads with a Q wave can give an immediate prediction of higher probability of microvascular damage.

Regarding the noninvasive imaging techniques, transthoracic echocardiography with intracoronary injection of echographic contrast (in the catheterization laboratory) initially represented a major advance in demonstrating conclusively the presence of myocardial perfusion defects in patients with an open epicardial artery. Due to the need to combine it with cardiac catheterization and its limited uptake in the catheterization laboratories, transthoracic echocardiography with intravenous injection of echographic contrast led, to some degree, to the more widespread use of totally noninvasive echocardiography for the study of this phenomenon. However, the interpretation of these studies requires extensive experience and the images are not always optimal.[3] Therefore, the contribution from CMR represented a landmark.

Currently, the analysis of late gadolinium enhancement is the reference standard for the diagnosis and quantification of MVO.[2,3,5] Minutes after contrast injection, gadolinium disappears from the myocardium. The persistence of late contrast uptake allows precise delimitation of the infarcted area, while a lack of contrast in the central region of the infarcted territory identifies severe microvascular dysfunction (MVO).[2,3,5] Other CMR-related methods, such as the delayed arrival of contrast to the infarcted area during the first pass after injection (very sensitive but not very specific for severe microvascular damage) or the quantification of myocardial flow (not yet validated), are alternatives to late uptake sequences for the assessment of MVO.[3]

Regarding the invasive imaging techniques, there are various visual and semiquantitative angiographic markers that are easy to use, traditionally used in the catheterization laboratory without prolonging the investigation. TIMI flow grade (a visual assessment of the filling rate of the epicardial artery), corrected TIMI frame count (which aims to quantify this filling rate) and myocardial blush grade (which determines the uptake of angiographic contrast in the territory of an epicardial artery) have been widely used in catheterization laboratories for the assessment of coronary perfusion.[2,3] These indices have considerable variability and are highly operator-dependent. The presence of abnormalities (especially a TIMI flow grade of 2 or less) is very specific for the detection of abnormalities in the microcirculation after reperfusion. However, up to 30% of patients with apparently normal flow in the coronary artery after revascularization (TIMI grade 3) have a reperfusion deficit on a reference technique such as CMR.[2,3]

More recently, new indices derived from cardiac catheterization have been described that allow reliable assessment of the microcirculation in different contexts from a more physiological approach. They provide a quantification of flow (such as coronary flow reserve, deceleration time of coronary diastolic flow or systolic flow reversal) or microvascular resistance.[2,3] The need to induce hyperemia by administering vasodilators such as adenosine or the use of Doppler wires or pressure or temperature sensors means that, to perform this quantification, the studies take longer, in patients who are already complicated and clinically unstable. Therefore, despite their reliability, their routine use in the analysis of microvascular damage after infarction is uncommon.

Clearly, the catheterization laboratory must play a central role in the detection and treatment of microvascular damage. Indices are needed that improve the diagnostic reliability of traditional angiographic indices, but with a simpler approach than the coronary physiology indices, that is, without prolonging the studies and without the need for additional invasive devices.

It is in this context that new indices may be incorporated, such as the index of microcirculatory resistance (IMR) evaluated on angiography (angio-IMR), which can provide immediate information on microvascular damage after revascularization without the need for additional intracoronary devices. This new parameter is based on biophysical assumptions and takes into account the aortic pressure, the length of the vessel, the flow velocity at rest (quantified using the TIMI frame count method) and the fractional flow reserve assessed on angiography.[6]

The article by Shin et al.,[6] published in *Revista Española de Cardiología*, showed in a cohort of 285 patients with STEMI (taking as a reference the presence of MVO on CMR) that 88.3% of those with an angio-IMR $>$ 40 U had microvascular damage in the acute phase, while this phenomenon only occurred in 32.1% in those with an angio-IMR$<$ 40 U. In addition, patients with an angio-IMR $>$ 40 U had worse structural findings on CMR: larger infarct size, lower ejection fraction, and more extensive MVO. The study also concluded that angio-IMR had greater discriminatory capacity than TIMI flow grade and myocardial blush for detecting MVO.[6]

We must congratulate the authors for validating this intuitive method, with a physiological profile, without the need for wires or hyperemic agents and with a higher diagnostic capacity for microvascular damage than the more commonly used angiographic indices. The quantification, if the appropriate software is available, is fast, with immediate analysis of the angiograms recorded during a standard procedure. Furthermore, for the validation of the parameter of microvascular damage, the authors used the presence of MVO on CMR as the reference. It should be noted, however, that its reliability it good but not excellent (more than 30% of patients with apparently normal angio-IMR had MVO on CMR). In addition, it would be ideal if this attractive index were validated (both for the diagnosis of MVO and for the prediction of clinical events) in a large multicenter study.

Nonetheless, angio-IMR represents a step in the right direction toward the early and intuitive detection of microvascular damage after infarction and contributes to broadening the focus beyond the epicardial coronary artery. The catheterization laboratory must play a pivotal role in this area: now, in the early detection and, in the future, to deliver treatments as adjuvants to reperfusion.[8] This is one of the final steps to complete the incredible advances in the knowledge and management of STEMI that have taken place over the past century. The presentation dynamics of microvascular damage are associated with 3 important aspects that make the catheterization laboratory the ideal setting for its diagnosis and subsequent treatment:

- Reperfusion is the critical point for saving both myocardium and microcirculation.[2,3,5] A longer delay drastically reduces the probability of recovery. Furthermore, this is the key moment in potential ischemia-reperfusion damage and in the acceleration of microvascular damage. At this time, the coordination of patient transfer (infarct code) and an excellent technical and medical management in the catheterization laboratory are essential.
- The wave of microvascular damage has a much slower propagation (the peak of damage is several days after reperfusion) than cardiomyocyte necrosis.[3,9] This offers a potentially longer window of time (compared with the just 4-6 hours available to save the myocardium) in which future adjuvant treatments, aimed at repairing microvascular damage, could act.[10]
- There is a natural tendency, both in experimental models and in patients with STEMI followed up sequentially with CMR, to spontaneous repair of the microcirculation during the weeks and

months after an infarction.[2,9] This tendency to spontaneous microvascular regeneration is in contrast to the practically nonexistent myocardial regeneration and is a natural response of the body that, properly understood and regulated, could represent an attractive therapeutic target in the future.

After a decades-long research effort, the advances in myocardial regeneration after infarction have been modest. In contrast, microvascular regeneration is a natural tendency in the body mediated by an orchestrated natural response aimed at neoangiogenesis.[9,10] This dynamic suggests that a better understanding of the process of microvascular damage could lead in the future to treatments involving regulation and controlled acceleration of microvascular repair for those patients who could benefit most, that is, those with severe microvascular damage.

The as yet unanswered question is which reperfusion-adjuvant products or strategies will be effective in clinical practice to complete this exciting journey that, over the last century or more, has led to improved prognosis in patients with STEMI. The answer will probably not be simple. Intuitive maneuvers that seemed certain to have immediate efficacy, such as thrombus aspiration or postconditioning, have been demonstrated to be insufficient. In contrast, as proof of concept, there are preliminary data that indicate that measures to selectively potentiate the microvascular damage repair process could help with reperfusion in an attempt to save myocardium and repair the microcirculation.[10] However, the translation to clinical practice of this type of approach will require further intensive research efforts. Meanwhile, reinforcement and increased reach of cardiovascular education, primary prevention measures, and early reperfusion strategies will strengthen all that has been achieved so far.

The study by Shin et al.[6] shifts the focus once more to microvascular damage in the catheterization laboratory. The availability of tools to allow early, reliable diagnosis of this phenomenon will be essential not only for diagnosis and risk stratification, but also to guide decision-making. It is likely that the safest and most effective way to apply potential reperfusion-adjuvant treatments will be their selective release in the center of the area of myocardial or microvascular damage using selective catheterization.[8] Therefore, the catheterization laboratory must be central to this.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the present article.

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