Although technical advances enable normal epicardial coronary artery blood flow to be restored in most patients suffering myocardial infarction, restoration of blood flow is not always followed by improved myocardial perfusion. Recently, therefore, interest in the assessment of myocardial perfusion has grown, and a number of different assessment methods are available. The aim of this article was to provide an evaluation of the additional information that can be obtained from the widely used technique of conventional coronary angiography. We present a review of the data on epicardial coronary artery blood flow (both semiquantitative and quantitative) and on microvascular blood flow that can be obtained using coronary angiography and discuss their prognostic significance.

Key words: Coronary angiography. Coronary blood flow. Myocardial perfusion.

INTRODUCTION

The main aim in treating acute myocardial infarction (AMI) is to restore patency in the epicardial coronary artery. The theory of the “open artery” is based on two fundamental factors: time (as soon as possible) and size (as much flow as possible). Whatever the reperfusion method used, as demonstrated in many studies, the final aim is that the angiographic parameter, epicardial blood flow, is normal. Given that the latest developments make it possible to restore “normal” epicardial flow in more than 90% of the patients and that, given this is achieved, a significant number of patients still have unresolved ST segment and their myocardial perfusion is not restored under myocardial contrast echocardiography (MCE), interest has shifted from the epicardial arteries towards myocardial perfusion. There are several methods to assess the state of coronary microcirculation and myocardial perfusion, from the simplest—analyzing a previously resolved ST-segment elevation in the electrocardiogram (ECG)—to the more complex—positron emission tomography (PET). The aim of this article is to review the findings obtained with coronary angiography to assess the quality of both epicardial and microvascular reperfusion.

RELEVANCE AND LIMITATIONS OF ASSESSING EPICARDIAL FLOW

Open Epicardial Artery: TIMI Flow Grading

The evaluation of blood flow in the epicardial coronary artery was formalized 20 years ago by the TIMI research group (Thrombolysis In Myocardial Infarction) with the so-called TIMI flow grades. Table 1 shows the characteristics of each grade. Many studies have demonstrated the correlation between this parameter and later events such as:

Coronariografía: más allá de la anatomía coronaria

Aunque los avances tecnológicos permiten restaurar el flujo coronario normal en la arteria epicárdica en la mayoría de los pacientes con infarto de miocardio, no en todos los casos se traduce en la mejora de la perfusión miocárdica; por ello, el interés clínico en la evaluación de ésta ha crecido recientemente. Son varios los métodos que permiten valorar este parámetro, pero el objetivo de esta revisión es analizar la información adicional que ofrece una técnica ampliamente usada, la simple coronariografía. Se revisan los datos de flujo epicárdico (tanto de forma semicuantitativa como cuantitativa) y microvascular que se pueden obtener con la coronariografía y su implicación pronóstica.

Palabras clave: Angiografía coronaria. Flujo coronario. Perfusión miocárdica.
reinfarction, 30-32 mortality, 2-6, 33, 34 free wall rupture, 35 development of ventricular aneurysm 36 or the appearance of arrhythmias. 37-40 This correlation with prognosis, which was initially described for thrombolytic treatment in acute myocardial infarction (AMI), has also been extended to percutaneous coronary intervention therapy (PCI). 39-44 This relationship has been shown to be so strong that TIMI 3 flow is normally used as a parameter to evaluate the efficacy of different treatments instead of the relevant clinical events. 43-52 This classification allows us to establish the superiority of TIMI 3 flow over other parameters, even over TIMI grade 2: 2 meta-analyses 33, 34 report that early mortality was significantly lower among patients with TIMI 3 flow at 90 min after fibrinolysis than in the group with TIMI 2 flow (3.7% vs 6.6%; odds ratio [OR] 0.55; 95% confidence interval [CI], 0.4-0.76) or than in group with TIMI 0 or TIMI 1 flows (9.2%; OR=0.38; 95% CI, 0.29-0.5). With the development of reperfusion therapy using PCI, the use of these predictors has continued to prove their validity, 41 although some studies point out that the difference in mortality between TIMI 2 and 3 grades might not be so marked nowadays with the use of invasive therapies that combine fibrinolytic drugs and PCI. 23 On the other hand, technical developments in the intervention field (e.g. stenting, 53, 54 thrombectomy devices, 55, 56 distal protection systems 57-60) have not been associated universally with an improvement in TIMI flow. Nevertheless, this grading system has some limitations:

1. The most relevant limitation is its subjectivity, which leads to important discrepancies, 61 even when

### TABLE 1. Epicardial Flow and Myocardial Perfusion Grading Systems

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epicardial blood flow: TIMI flow grades (TFG)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Absence of anterograde flow after the occlusion point</td>
</tr>
<tr>
<td>1</td>
<td>The contrast agent passes through the occluded area, without opacifying the entire length of the artery by the end of the injection</td>
</tr>
<tr>
<td>2</td>
<td>The contrast agent opacifies the entire artery, but is remarkably slower in the non-culprit arteries or in the area proximal to the occluded section of the artery. A later subclassification distinguishes between grade 2a (slow filling, within 5 heart beats), grade 2b (slow filling in more than 5 heart beats) and grade 2c (normal filling, slow washout)</td>
</tr>
<tr>
<td>3</td>
<td>Normal anterograde flow and contrast clearance, similar to those in non-culprit arteries or proximal to the occluded section of the artery</td>
</tr>
<tr>
<td>4</td>
<td>Anterograde flow and clearance of contrast is faster than in non-culprit arteries</td>
</tr>
<tr>
<td><strong>Microvascular flow: TIMI myocardial perfusion grades (TMPG)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Absence or minimum blush of the myocardium in the distribution section of the culprit artery</td>
</tr>
<tr>
<td>1</td>
<td>Persistent myocardial blush, the contrast agent enters the microvasculature, but it does not normally pass to the venous phase: “persistent stain” is detected at the beginning of the next injection (&gt;20 s)</td>
</tr>
<tr>
<td>2</td>
<td>Delayed blush and washout of the myocardium: in the myocardial stain is evident (maximum level) or minimum decline in intensity) by the end of the injection (3 heart beats for washout)</td>
</tr>
<tr>
<td>3</td>
<td>Normal blush: entry and exit of the contrast agent from the microvasculature at normal speed (total or high washout of the dye within 3 heart beats)</td>
</tr>
<tr>
<td><strong>Microvascular flow: myocardial blush grades (MBG)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Absence of myocardial blush or “persistent stain,” indicative of the contrast exiting the extracoronary space</td>
</tr>
<tr>
<td>1</td>
<td>Minimal myocardial blush</td>
</tr>
<tr>
<td>2</td>
<td>Moderate myocardial blush, of smaller intensity than in the reference area supplied by the non-culprit ipsilateral or contralateral artery</td>
</tr>
<tr>
<td>3</td>
<td>“Normal” myocardial blush, similar to the reference area</td>
</tr>
</tbody>
</table>
2. El tiempo de llenado del arteria coronaria descendente anterior (LAD) está más alto que en otras arterias, ya que es generalmente la más larga. Dado que el llenado de esta arteria se puede comparar simultáneamente con el llenado de la arteria circunfleja, la tendencia a asignar un grado TIMI 2 es mucho mayor con la arteria coronaria descendente del lado derecho (RCA). 64

3. El grupo TIMI ha modificado (sin mucha aceptación) el sistema de graduación para destacar hasta 3 subgrupos en TIMI 2 65 (Tabla 1). Estos cambios incluyen factores como la velocidad de descarga que se discuten más adelante.

4. Finalmente, no podemos descartar la presencia de factores que podrían significativamente modificar la graduación, como la presión y fase del ciclo cardíaco en el momento de la inyección de contraste, el ritmo cardíaco y la presión arterial del paciente, el uso de disolventes, etc. El impacto de estos factores se discute en la próxima sección.

**Open Epicardial Artery: Quantification. Corrected TIMI Frame Count**

En el contexto de los posibles límites de la graduación TIMI, se han desarrollado sistemas de evaluación más detallados que mejor caracterizan el flujo y mejoran la reproducibilidad de los resultados: el sistema de cuenta de marcos TIMI corregida (cTFC) desarrollado por Gibson et al 64 es el más ampliamente validado.禀

Basicamente, cuantifica el grado TIMI de flujo midiendo el tiempo que lleva al contraste llenar por completo la longitud de la arteria epicárdica. Para standardizar los criterios, se definen varios bifurcaciones distales como marcadores finales: el "cola del ballena" en la punta de la LAD, la longitud total de sección donde la sustancia viaja en el sistema circunflejo y que pasa a través de la lesión causante, y la primera bifurcación del arteriopecho lateral en la arteria coronaria derecha (Figura 1). La diferencia en el número de marcos entre el último y el primero (donde el contraste llena al menos el 70% de la arteria y comienza a moverse en dirección antero) constituye el TIMI frame count. Algunos de los aspectos metodológicos de este sistema se discuten en las siguientes secciones:

1. Como se describió,64 el largo de la LAD es un 1.7 veces mayor que el circunflejo y la arteria coronaria derecha. Por lo tanto, se introdujo un factor de corrección en el sistema TFC cuando se analiza la LAD: el cTFC es el resultado de la diferencia absoluta dividida por el factor de corrección, 1.7.

2. Todos los valores publicados inicialmente como "cuentas de marcos" referirse al formato de video del United States, NTSC: 30 frames per second. En orden
TABLE 2. Values of the Corrected TIMI Frame Count (by Number of Frames)

<table>
<thead>
<tr>
<th>Normal Values (Healthy Volunteers)</th>
<th>TIMI 3 Flow (After Infarction)</th>
<th>TIMI 4 Flow (After Infarction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 frames/s</td>
<td>&lt;21</td>
<td>&lt;14</td>
</tr>
<tr>
<td>25 frames/s</td>
<td>&lt;18</td>
<td>&lt;12</td>
</tr>
<tr>
<td>12.5 frames/s</td>
<td>&lt;8</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Seconds</td>
<td>&lt;0.7</td>
<td>&lt;1.3</td>
</tr>
</tbody>
</table>

TABLE 2. Values of the Corrected TIMI Frame Count (by Number of Frames)

2. This is an easy method that does not require special equipment and can be performed immediately after capturing angiographic images.

3. The cut-off points shown in Table 2 allow us to classify unclear epicardial flows.

Nevertheless, the method presents certain limitations as it has been found that some factors can significantly change the values calculated:

1. Heart rate. An increase of 20 heart beats/min shortens the count by 5 frames. 80
2. Using nitrates increases the count by 6 frames. 80
3. Injecting during the protodiastolic period reduces the count by 3-6 frames. 80
4. When the LAD is the culprit artery of the infarction: in such cases the count is higher than in the other arteries by 8 frames, even after correcting for length and adjusting for other variables. 80

It has not been demonstrated whether the calculation is affected by patient-dependent factors (e.g. age, sex, body size, blood pressure, or cardiovascular risk factors) or by procedure-dependent factors (injection pressure or type of contrast agent). 80

Taking this method as a basis, another assessment system has been developed, not only for the epicardial blood flow, but also for microcirculation flow—the assessment of the coronary blood flow reserve by analyzing the relationship of cTFC at baseline and cTFC after the administration of contrast agents (e.g. adenosine). 74,86 Although other studies have not confirmed this. 77

ASSESSMENT OF MYOCARDIAL PERFUSION AND MICROCIRCULATION

Open Microvasculature: Assessment. Myocardial Blush

Since the classic descriptions of reperfusion injury and no reflow events were presented, 7,8 the attempts to assess the state of myocardial perfusion after an infarction have increased. The resolution of the ST-segment is the simplest and most reproducible analysis. Another method widely used is the MCE, which, apart from being a non-invasive method, can be quantified. In both cases, the results have been correlated with the appearance of subsequent events. 68-72, 74-76

With the increasing implementation of PCI as the treatment of choice for AMI, the availability of an early angiography is quite frequent and this has permitted the development of the myocardial blush...
TABLE 3. Treatment of Suboptimal Myocardial Perfusion

<table>
<thead>
<tr>
<th>Drug/Method</th>
<th>Result</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>Positive</td>
<td>Small studies(^{104-106})</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Positive</td>
<td>Small studies(^{111,112})</td>
</tr>
<tr>
<td>Cariprol (Na(^+) pump inhibitor)</td>
<td>Negative</td>
<td>GUARDIAN Study(^{113})</td>
</tr>
<tr>
<td>Intracoronary adenosine</td>
<td>Positive (subgroup)</td>
<td>AMISTAD II Study(^{114})</td>
</tr>
<tr>
<td>Abciximab (glycoprotein IIb/IIIa inhibitors)</td>
<td>Positive</td>
<td>Several studies(^{115-117,118,119})</td>
</tr>
<tr>
<td>Pexelizumab (complement inhibitor)</td>
<td>Pending</td>
<td>APEX AMI Study(^{120})</td>
</tr>
<tr>
<td>HU23F2 (antibody anti-CD18)</td>
<td>Negative</td>
<td>HALT-AMI Study(^{121})</td>
</tr>
<tr>
<td>Gefaplermin (eGFR overload inhibitor)</td>
<td>Pending</td>
<td>EVOLVE Study(^{122})</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Non-conclusive</td>
<td>Preliminary studies(^{123,124})</td>
</tr>
<tr>
<td>Aqueous hyperoxygenation</td>
<td>Non-conclusive</td>
<td>Preliminary studies(^{125})</td>
</tr>
<tr>
<td>Thrombectomy devices</td>
<td>Positive</td>
<td>Small studies(^{126,127,128})</td>
</tr>
<tr>
<td>Distal protection devices</td>
<td>Negative</td>
<td>EMERALD Study(^{129})</td>
</tr>
</tbody>
</table>

The assessment of myocardial blusl has its own limitations:

1. The qualitative character of this parameter makes it inherently subjective. Thus, intra- and inter-observer consistency is limited, as described by one of the groups with the greatest experience.\(^{130}\) In most studies, the analysis of MBG or TMPG is performed in central laboratories, and thus, the consistency with the assessments carried out by other observers might not be suitable.

2. Many of the studies carried out tend to group patients with MBG 2 and 3 or TMPG 2 and 3 into a single group with suitable perfusion. Given that it has been demonstrated that the prognosis of patients with TIMI 2 and TIMI 3 flow is not equivalent, this simplification of the system is most probably wrong.

3. Nevertheless, the fundamental limitation is not methodological, but refers to the unsolved challenge of treating suboptimal myocardial perfusion after coronary reperfusion. Table 3 sums up evidence published in this domain.

The correlation between the analysis of ST-segment resolution and myocardial blush is controversial because, although both have been related to clinical events, they do not always seem to match in every patient. What could be interpreted as a limitation tends to be assessed as another “anomalous” event, which are not uncommon in cardiology: the “electrical recovery” shown in the ECG is not always associated with integrity of the microvascular endothelium and recovery of perfusion, and vice versa. In fact, the 2 methods are complementary when the size of the infarction,\(^{131}\) or the angiography are analyzed. Their complementarity is also shown by the fact that the...
There is ample literature available on the correlation between MCE and angiography, although a perfect correlation is not always found, even though both methods, at least theoretically, analyze myocardial perfusion. Bearing in mind that this is a dynamic event (some days after the infarction, many patients that initially did not show suitable myocardial blush may show a much better grade), the discrepancies may be due to the behavior of the different contrast agent used—echographic contrast agents (microbubbles) always remain in the intravascular space, whereas radiological contrast media (and paramagnetic contrast used in magnetic resonance) often present extravascular passage, subsequently returning to the bloodstream. Thus, some authors argue that angiography or magnetic resonance do not actually assess myocardial perfusion, but rather capillary patency, the state of the endothelium, and the edema and interstitial hemorrhage i.e. reperfusion injury.

Figure 2. Examples of myocardial perfusion analysis. A: persistent stain of the septum ( delimited by the arrows); grade 1 myocardial perfusion (TMPG), grade 0 myocardial blush (MBG) in LAD. B: persistent myocardial stain in the diaphragm territory; TMPG 1, MBG 2 grades in RCA. C: persistent capillary stain (small vessels are visualized) in RCA. D: lower intensity stain than in left coronary artery in the diaphragmatic territory (black arrow, TMPG 2 and MBG 2 grades) and barely present in posteroanterior (white arrow, TMPG 0.5 and MBG 1 grade). E: normal myocardial stain (TMPG grade 3 and MBG grade 3) of left coronary artery. A donut-like image in LAO cranial projection. F: normal myocardial stain (TMPG 3 and MBG 3 grades) of RCA; example of digital subtraction (DSA).
Myocardial perfusion assessed by angiography is analyzed by using several quantitative methods:

1. Methods based on digital subtraction angiography (DSA), widely used in vascular radiology, but little used in coronary angiography, may facilitate the quantification of the opacified area (in theory, this is “equivalent” to areas quantified in MCE), blush intensity (“MBG quantification”) or the speed at which the blush appears or disappears (“TMPG quantification”). For DSA to be more applicable, several studies are working on the development of techniques, such as moving mask, to attempt to neutralize the movements inherent to the heart.

2. A quantification system, based on cTFC has been suggested. This quantifies the number of frames between the entrance of the contrast agent into the myocardium and the peak blush intensity: the TIMI myocardial frame count. This count is significantly greater in patients with AMI with ST-segment elevation than in patients with NSTEACS.

3. Our group has developed a quantification system known as the Coronary Clearance Frame Count (CCFC) with good correlation with TMPG grades. Defined as “the inverse of cTFC,” it counts the difference in frames between the moment in which the contrast agent enters the myocardium and the peak blush intensity.

Figure 3. Mortality after AMI and myocardial blush grades. A: mortality rate in relation to the myocardial blush grade at 1 month (Gibson et al) and in the longer term (follow-up 1.9±1.7 years [van’t Hof et al]) and after 1 year (Stone et al). B: mortality in relation to the myocardial blush grade in the patients with TIMI 3 flow in the culprit artery: at 1 month (Gibson et al) and after 1 year (Stone et al). TMPG: TIMI myocardial perfusion grade; MBG: myocardial blush grade.
contrast disappears from the arterial ostium and when it begins to disappear from the distal bifurcation described in the cTFC system. Although its potential clinical relevance has not been established yet, it shows correlation with myocardial perfusion TMPG grade 2 or 3, creating a cut-off point (45 images) that makes it possible to differentiate the better perfusion grades.

cTFC Analysis and Myocardial Blush. Practical Considerations

Both the quantitative analysis of epicardial blood flow (cTFC) and microvasculature flow can be carried out online with current digital equipment, or offline with software for image review. Nevertheless, if the imaging conditions are not optimal, the interpretation and later analysis may be biased. Thus, some standard recommendations are made:

1. Imaging field: 23 cm. Not magnifying the image enables recording the whole length of the artery without the need for panning. This is particularly important for the correct analysis of myocardial blush, especially when DSA is used. The quality of current DSA images (fixed mask) is also highly dependent on maintaining a proper image during the recording.

2. Imaging speed: ideally, 25 frames/s. Nevertheless, cTFC can be calculated at any recording speed, and subsequently it can be expressed in seconds or minutes adjusted to the recommended speed.

3. Recording time: up to the appearance of contrast in the venous phase. This is very relevant for the TMPG analysis system. In this case, it is also particularly important to leave at least 3 seconds between one injection and the following one, and not to record immediately after contrast tests (it may incorrectly assign TMPG 1 values).

4. Selective projections:

a) Analysis of cTFC. Recording images in PA or RAO projection (0°-30°) is recommended with caudal angulation (20°-30°) for the left coronary artery and in LAO projection (45°-60°) for the right coronary artery.

b) blush analysis: the recommended projections differ from the previous ones, especially in the left coronary artery, where perfusion territories may be seen as overlapping. Thus, LAO projection (45°-60°) is recommended with cranial angulation (20°-30°), which makes it possible to see a donut-like image, or a left lateral projection (90°) in the case of the left coronary artery; for the right coronary artery, an LAO projection is recommended (45°-60°) with or without cranial angulation or RAO (30°).

From a practical point of view, in our center we systematically analyze myocardial perfusion data from angiographies (according to both the TMPG and the MBG system) in all cases of angioplasty within the context of AMI and in other cases of intervention with no reflow events or slow final blood flow, reserving cTFC and CCFC for cases with TIMI blood flow or perfusion. In all these cases, the information obtained is always complemented by electrocardiographic analysis of ST-segment resolution.

CONCLUSIONS

Coronary angiography offers relevant but simple and easy to interpret information, not only on the state of the epicardial coronary circulation (TIMI flow in the epicardial artery and its quantification, TIMI frame count), but also on the state of microvascular circulation (myocardial blush grades: TIMI myocardial perfusion and myocardial blush grades). These data allow us to reliably assess the patient’s prognosis. The development of a quantitative variant of these techniques could improve their predictive power.

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