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Chapter

Primary Angioplasty: From the Artery to the Myocardium

Miguel Angel Farah, Franco Farah and Miguel Alejandro Farah

Abstract

The prognosis of patients suffering from acute myocardial infarction (AMI) is related to the amount of muscle loss and ventricular function deterioration caused by the event. Primary angioplasty is the most effective reperfusion strategy. Early reperfusion limits the size of the infarction and improves the prognosis. However, the incidence of death and post-AMI heart failure remains around 20% during the first year. Factors that contribute to myocardial damage are ischemia, mechanical forces, inflammation, and reperfusion injury. All those take a variable and sometimes unpredictable preponderance at different times during the evolution of acute myocardial infarction. The damage caused by the different mechanisms is irreversible; therefore, any therapeutic strategy must be preventive. Developed treatments for continuous myocardial protection could potentially preserve the myocardium during the delay of the system and during the early evolution of the event. Developed controlled reperfusion procedures where the interventional cardiologist assumes the treatment not only of the culprit vessel but also of the myocardium could potentially decrease myocardial damage, preserve ventricular function, and improve patients' prognosis.

Keywords: myocardial damage, acute myocardial infarction, ischemia, mechanical forces, inflammation, reperfusion injury, continuous myocardial protection, controlled reperfusion

1. Introduction

The prognosis of patients suffering from acute myocardial infarction (AMI) is directly related to the amount of muscle loss and the deterioration of ventricular function caused by the event [1–4]. Consequently, the goal of treatment in the initial phase, beyond preserving life, is to limit myocardial damage. Early reperfusion of the myocardium limits the size of the infarction and improves the prognosis of patients [3, 4]. Primary angioplasty is the most effective reperfusion strategy for the treatment of acute myocardial infarction [5–7]. From the first reports of mechanical reperfusion to the present, the primary angioplasty strategy continuously improved in different aspects such as greater accessibility to the method [8–10], safer vascular accesses [11, 12], and the use of drug-eluting stents that modulate the scarring of the coronary artery wall [13, 14] to prevent restenosis of the vessel or vessels treated. In addition, the development of antithrombotic and antiplatelet drugs also

contributed to improving early and late artery permeability [15, 16]. The enormous effort focused on the treatment of the coronary artery has led to the fact that the success of primary angioplasty is now greater than 95% [7]. The angiographic success rate ceased to be a problem. However, the post-AMI incidence of death and heart failure remains around 20% during the first year [17], and as mentioned earlier this correlates directly with the amount of myocardium damaged and the deterioration of ventricular function.

2. The following case serves to illustrate the result of AMI usual treatment at present

52-year-old male, with grade II obesity, dyslipidemia, hypertension, and smoking history and with no previous cardiovascular events, arrives at the hospital 60 minutes after the onset of symptoms. The first electrocardiogram (ECG) shows rS in V1, V2, and V3 and ST-segment elevation from V1 to V6 (**Figure 1**).

At admission the arterial blood pressure was 145/80 mm of hg, the heart rate was 78 beats per minute, and the Killip Kimball grade was A. The patient received aspirin (250 mg), clopidogrel (600 mg), unfractionated heparin in intravenous bolus (5000 UI), and rosuvastatin (40 mg). At 80 minutes after admission, 140 minutes from the onset of symptoms, coronary angiography is performed showing single-vessel disease with thrombotic occlusion of the middle third of the anterior descending artery (ADA) and TIMI 0 flow. Primary angioplasty is performed to the middle third of the ADA with thromboaspiration and stent implantation achieving an adequate result with TIMI 3 flow, symptom relief, and absence of complications.

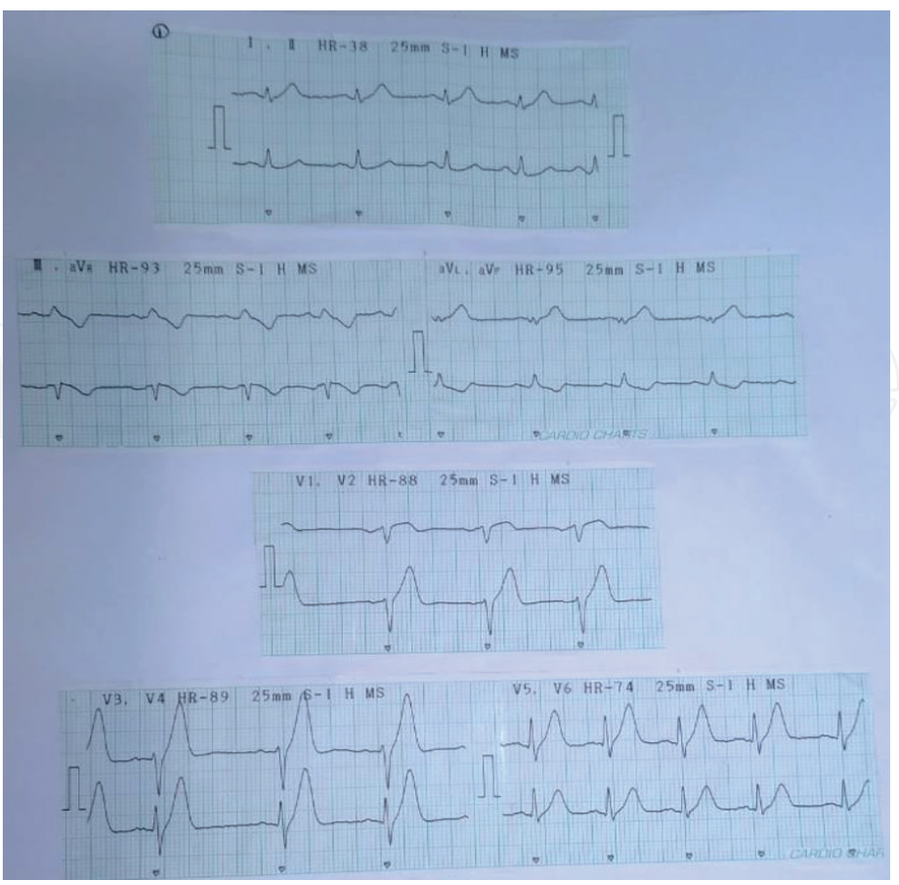

Figure 1.
ECG at admission.

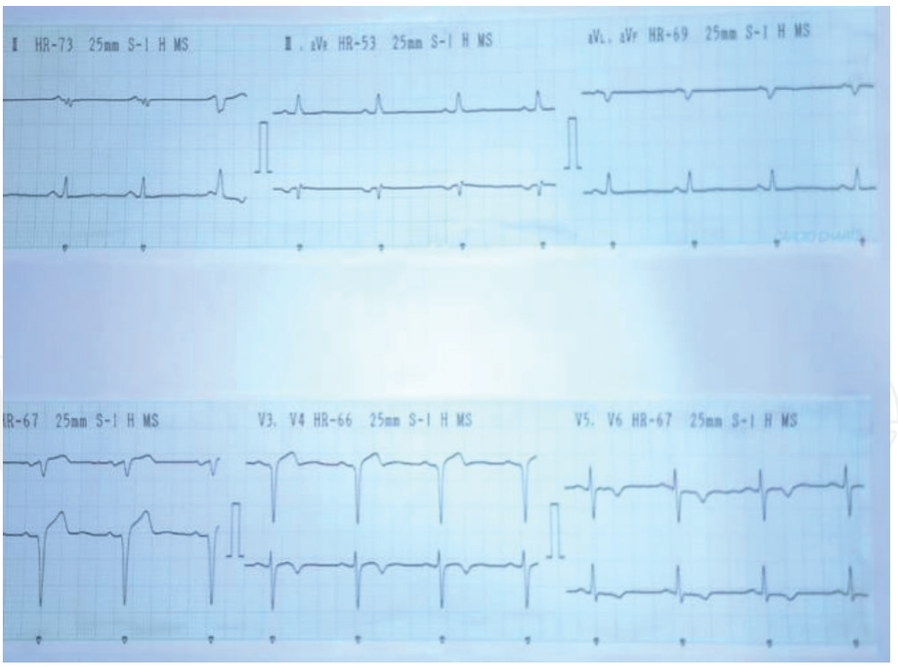

Figure 2.
ECG postprimary angioplasty.

The post-procedure ECG shows QS in V1, V2, and V3 and ST level and negative T from V1 to V6 (**Figure 2**).

IECA and B blockers are started. It evolves without recurrence of symptoms; however, at 48 hours, the ECG shows QS from V1 to V5 and low R in V6 (**Figure 3**).

Note that despite early assistance, it no longer has positive vectors in V1, V2, and V3, and after the usual successful treatment and aligned with the guidelines based on current evidence, it continues to lose precordial vectors after primary angioplasty. The echocardiogram shows antero-apical dyskinesia and impaired ventricular function, with an ejection fraction of 35% measured by the Simpson method. There are several mechanisms by which the myocardium is lost in the different phases of AMI.

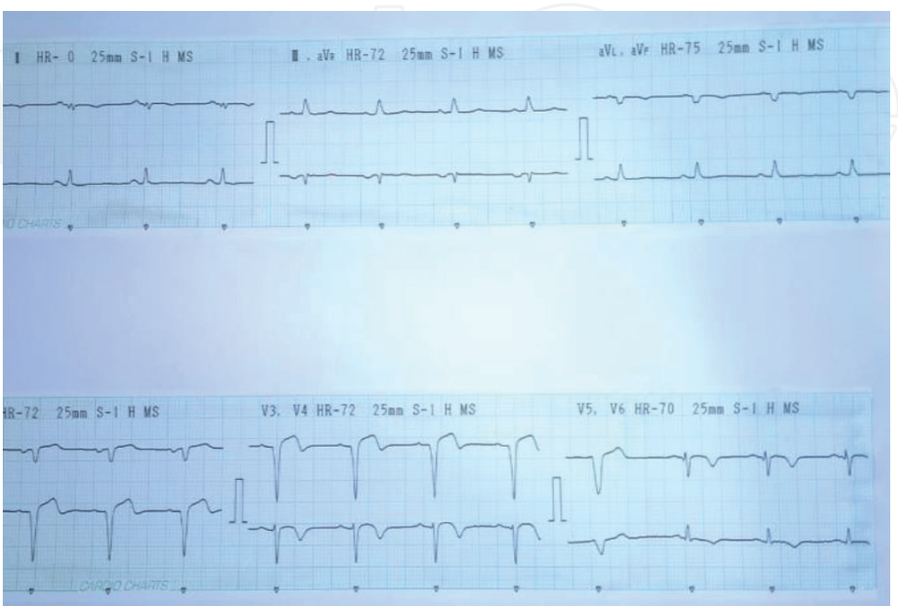

Figure 3.
ECG at 48 hours.

3. Etiopathogenesis of myocardial damage

The factors that contribute to myocardial damage are as follows:
Ischemia.
Mechanical forces.
Inflammation.
Reperfusion injury.

3.1 Ischemia

It implies the interruption of blood flow, the supply of O_2 and nutrients. The myocyte stops producing ATP from the fatty acid oxidation and switches to another metabolic pathway that is suboptimal not only because it cannot maintain a balance between nutrient supply and demand and O_2 but also because of the accumulation of metabolic wastes that this route produces, and that generates an environment harmful to the subsistence of the cells and the appropriate reperfusion, favoring the phenomenon of reperfusion injury [18]. The alternative route for ATP production during ischemia is anaerobic glycolysis; its potential to produce ATP is 20 times less than aerobic glucose metabolism and even less than the route commonly used by myocyte which is the aerobic metabolism of fatty acids. The glycogen reserve as a source of anaerobic ATP is depleted in 30–60 minutes and also generates lactic acidosis, high concentration of protons at tissue level, and excess of H_2O. The mechanisms of myocardial damage due to ischemia involve low production of ATP that is insufficient not only for myocyte function but also to preserve its structure and to maintain hydroelectrolytic balance by the Na-K ATPase pump, which implies an increase in Na and intracellular H_2O with tissue and cellular edema, vacuolization, and cell burst [19, 20]. Inactivation of the Na-K ATPase pump leads to the activation of the Na-Ca exchange, resulting in increased intracellular calcium with hypercontraction of myocytes (contraction band necrosis) [21, 22]. The entry of Ca into the cell is one of the mechanisms by which the permeability of the transition pores of the mitochondria increases and their destruction occurs [23]. Myocardial ischemia can be either primary before applying reperfusion therapy or secondary, that is, after recanalizing the occlusion. As for primary ischemia, it can occur in a sustained or episodic manner. In some cases, episodic primary ischemia can generate a protective myocyte phenomenon known as ischemic preconditioning [24]. The mechanical factors that produce arterial occlusion and primary ischemia are plaque thrombus, and vasospasm. Secondary ischemia is always harmful and may be due to failed angioplasty, no reflow phenomenon, distal embolism, thrombotic reocclusion, post-reperfusion, vasospasm, etc. Consequently, myocardial ischemia occurs from the onset of AMI and may end with primary angioplasty, or persist (not reflow), or recur after it.

3.2 Mechanical forces

The ischemic myocardium stops contracting and is distended; this situation subjects it to exceptional mechanical forces of tension, traction, and stretching. In each systole, the nonischemic myocardium, which acts in a state of compensatory hypercontractility, pulls on the edges of the ischemic myocardium. In addition, in each systole, the healthy myocardium presses the blood against the ischemic myocardium causing distension and increased wall tension [25]. These forces of stretching and traction produce direct tissue damage [26] but also by increasing the tumor necrosis factor trigger mechanisms of apoptosis [27] dependent on caspases that produce cell death in early and late stages of AMI. The strongest evidence of the

damage that mechanical forces can produce is the rupture of the ventricular wall. As they are direct forces exerted on the ischemic myocardium, it is to be assumed that the damage is related to the magnitude and frequency of exposure; therefore, the higher the heart rate and inotropism, the greater the damage produced by this mechanism. This mechanism of myocardial damage begins immediately after the onset of ischemia and lasts beyond reperfusion.

3.3 Inflammation

The inflammatory response during the acute ischemic event plays a decisive role in the size of the infarction and the subsequent adverse left ventricle remodeling [28]. The onset of myocardial ischemia during AMI triggers a pro-inflammatory response whose initial objective is to eliminate damaged cells and tissue from the injured area. This initial pro-inflammatory phase contributes to myocyte death and tissue damage [29, 30]. This phase is followed by a repairing anti-inflammatory stage that leads to healing. Balance alterations and the transition between the pro-inflammatory phase and the anti-inflammatory phase can increase myocardial damage during the event and contribute to an adverse left ventricle remodeling after AMI [28]. In addition, the inflammatory response as an acute phase reactant is related to the location and size of AMI. Large and anterior infarct shoots a greater extent of acute phase reactants. The initial pro-inflammatory phase includes complement cascade activation and reactive oxygen species (ROS) production [28]. The damage-associated molecular patterns (DAMPs) production that binds to receptors in membranes cell and cytosolic proteins (inflammasomes), in either, circulating or myocardium resident cells. Inflammasomes cause caspase activation (which initiate the pyroptosis phenomenon, [apoptosis, and inflammatory necrosis]) and release pro-inflammatory cytokine as such as IL-1 and IL-8 and chemokines that recruit pro-inflammatory cells (polymorphonuclear, monocytes, macrophages, T and B lymphocytes) [28]. In addition, the inflammasomes activated during AMI induce ATP loss from the injured cells to the extracellular space, K outflow, lysosomal destabilization, and ROS generation by the mitochondria [28]. The anti-inflammatory phase begins with neutrophil and dendritic cell arrival; these cells secrete anti-inflammatory cytokines such as IL-10 and tissue growth factors that begin damaged tissue repair [28]. Monocytes and macrophages induced by interferon change their phenotype towards anti-inflammatory expressions [28]. Dendritic cells secrete chemotactic substances for regulatory T lymphocytes (CD4, CD25, and FOXP3) and T helper lymphocytes; these lymphocyte subtypes also secrete anti-inflammatory and reparative substances such as IL-10 and tissue growth factor and also induce the expression of anti-inflammatory macrophage phenotypes [28]. Although it is not proven, it is speculated that they could also activate pre- and post-conditioning mechanisms [28]. This myocardial damage mechanism is triggered in early stages after the onset of ischemia and continues beyond reperfusion.

3.4 Reperfusion injury

Myocardial reperfusion can itself produce more damage and cell death; this process defines the phenomenon of reperfusion injury [31–33] that could be prevented by applying additional therapies [34]. Reperfusion injury could be responsible for up to 50% of the final myocardial damage during acute myocardial infarction. The time elapsed since the onset of symptoms, diabetes, TIMI 0 flow in baseline angiography, DA involvement, and presentation with heart failure is associated with a greater chance of presenting reperfusion injury [35]. Elevation of white blood cells, greater activation (platelet size and reactivity), high levels of thromboxane

A2 and ET1, hyperglycemia associated or not with diabetes, and C-reactive protein before reperfusion are predictors of this phenomenon [36–38]. It is possible that there is always some degree of reperfusion damage, but the patients with little time of evolution of the symptoms and those who presented previous angina seem less susceptible [39, 40]. There is a useful premise to estimate its magnitude; the greater and more intense the ischemia, the greater the reperfusion injury [35, 41–43]. In daily practice, the lack of resolution of the ST segment after achieving epicardial coronary flow is used as a marker of reperfusion failure. In patients who do not correct the ST, the mortality of AMI triples beyond achieving adequate epicardial flow [44, 45]. The most important events that occur during reperfusion and trigger mechanisms of injury are the steep increase in oxygen content in a medium with a low PH (tissue acidosis caused by ischemia). In this scenario, O_2 binds to hydrogen protons generating reactive oxygen species that by themselves generate DNA, protein, and lipid damage to the membranes and consequently direct cell death [46, 47]. Besides, reactive oxygen species have pro-inflammatory effects mediated by cytokines that cause apoptosis and cellular necroptosis [48]. At the level of the mitochondria, ROS causes the opening of the transition pores of their membranes making them susceptible to irreversible damage [48]. At the endoplasmic reticulum level, the damage caused by ROS alters the dynamics of calcium, which in the context of reperfusion of an acidotic environment generates calcium entry into the sarcolemma, producing sustained hypercontraction that results in necrosis with contraction bands [47–49]. The calcium entry activates Ca-dependent proteases that degrade structural components of the cell [50]. The reperfusion injury affects not only the myocyte but also the microvasculature, where ROS not only produces direct damage to the endothelial cells causing increased permeability of the capillary wall resulting in edema but also is chemotactic for neutrophils, activates complement, and triggers pro-thrombotic phenomena [48–51]. In brief, microvascular occlusion occurs due to perivascular edema, cluster of neutrophils, and local thrombosis. Injury due to reperfusion occurs due to the arrival of saturated O_2 blood to myocardial tissue that is vulnerable to metabolic changes and the local internal environment, which occurred during ischemia. Reperfusion injury is a rapid and irreversible phenomenon [52].

The phenomena of ischemia, damage due to mechanical forces, inflammation, and reperfusion injury take a variable and sometimes unpredictable preponderance at different times during the evolution of AMI (**Figure 4**).

Also, the damage caused by the different mechanisms is irreversible; therefore, any therapeutic strategy must be preventive that implies pathophysiological

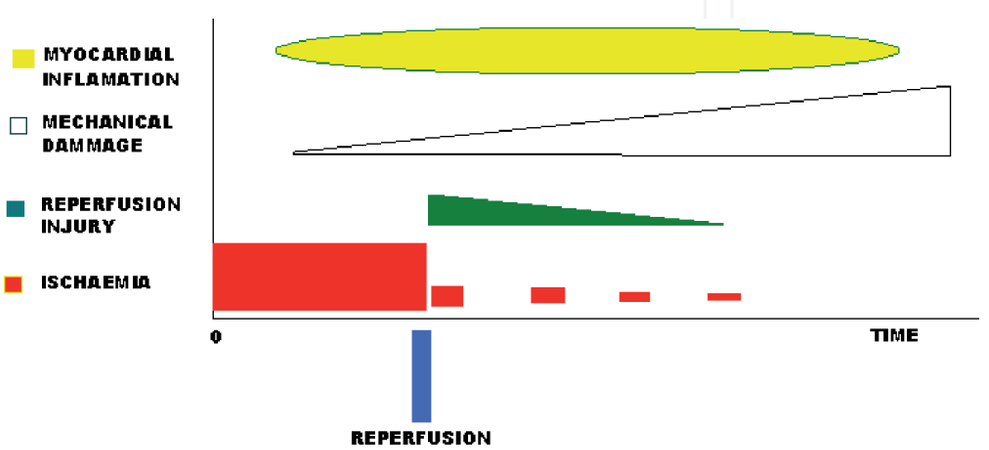

Figure 4.
Myocardial damage mechanism, importance, and development over time.

conditions that culminate in myocardial damage and act before the point of no return in the viability of the cell occurs.

4. Analysis of guidelines for AMI treatment

Both the AHA-ACC guidelines and the ESC guidelines for AMI treatment are strongly oriented to early and sustained reperfusion, which constitutes the most powerful resource for improving prognosis and saving lives during the event. The best way to show successful post-PCI or thrombolytic reperfusion is to verify the correction of the ST segment of the ECG performed after reperfusion therapy. Approximately 30% of patients receiving primary angioplasty in a timely manner do not correct ST elevation or initially correct it but continue to lose positive ECG vectors after apparently successful reperfusion. As we saw in the previous section, this happens because there is myocardial damage before, during, and after reperfusion [53]. However, the analysis of the guidelines shows that measures to reduce myocardial damage beyond reperfusion are poorly developed. The related items found in the current guides are reproduced below.

4.1 AHA-ACC guides 2013

4.1.1 Nitroglycerin

It improves the conditions of pre- and post-load of the ventricle and could also improve collateral flow and reduce BP which would improve the imbalance between supply and demand of O_2 in some patients. Based on the evidence provided by a meta-analysis that included 22 clinical trials and more than 80,000 patients, 3 or 4 deaths could be avoided per 1000 treated patients, which implies a net benefit. Nitroglycerin is a class I indication with a level of evidence C for patients with ischemic pain, hypertension, or pulmonary congestion [54].

4.1.2 B blockers

During the first hours of AMI, the B blockers can decrease the demand for O_2 by the myocardium by decreasing heart rate, blood pressure, and contractility and, additionally, by prolonging diastole, can improve ischemic myocardial perfusion, mainly of the subendocardium. As a consequence of this, B blockers can reduce the size of the AMI. Based on the clinical evidence provided by the ISIS I, MIAMI, TIMI II, and Taste I trials, the use of B blockers early, in the absence of contraindications, may offer benefits from the first day and in a sustained way avoiding around 6 deaths per 1000 patients treated. B oral blockers have class I indication level of evidence A, and in the form of intravenous administration, they have class IIa indication with level of evidence B [55–57].

4.1.3 Metabolic control

The metabolic modulation of the insulin glucose axis by infusion of glucose-insulin-potassium was evaluated in different trials with diverse and contradictory results that when taken together result in an intervention without net benefit compared to placebo. However, these guidelines suggest that it could be of benefit in patients with less than 12 hours of evolution, in Killip Kimball. Beyond that, the guidelines do not establish an indication with a level of evidence defined for this intervention [58].

4.1.4 Glycemia control

During AMI, the levels of catecholamines and cortisol increase, insulin decreases, and blood glucagon increase. This leads to a notable increase in blood glucose and decreased glucose utilization by cells. Free fatty acids and their metabolites are increased that increase myocardial damage by different mechanisms (direct inhibition of glucose oxidation, increased demand for O_2, direct toxicity). Insulin can reverse some of these mechanisms by inducing the production of ATP from aerobic glucose metabolism in the myocyte. Several studies mentioned in these guidelines demonstrated benefits in patients with hyperglycemia who received insulin infusion for strict glycemic control during the event. These guidelines establish that the normalization of insulin glycemia is a class I indication with a level of evidence B for patients with complicated AMI and class IIa with a level of evidence B for patients with uncomplicated AMI [59–61, 62].

4.2 ESC guides 2017

These guidelines mention, scarcely, that to reduce myocardial damage beyond reperfusion therapy, some strategies that include pharmacological and mechanical therapies have been demonstrating the potential to reduce the size of AMI by decreasing the impact of reperfusion injury in small clinical trials. But there is no large-scale clinical study that has demonstrated clinical benefit. Therefore, they make no recommendation regarding measures to limit reperfusion injury or any other therapy to reduce myocardial damage during the event, beyond reperfusion [63].

5. Current reperfusion adjuvant therapy status

The use of B blockers and nitrates is favorable to reduce myocardial damage caused by primary and secondary ischemia, reducing the imbalance between supply and demand of O_2 and nutrients until reperfusion. Beside, these drugs are useful to optimize the conditions of pre- and post-loading of LV, decrease heart rate and blood pressure, and thus limit the damage caused by mechanical stress. A wide variety of potent platelet antiplatelets such as clopidogrel, prasugrel, or ticagrelor added to the routine use of aspirin were shown to reduce the recurrence of ischemic events after reperfusion (secondary ischemia). Although it is not clearly established by evidence from clinical trials, thromboaspiration; potent vasodilators at the microvasculature level such as adenosine and calcium blockers, among others; and the use of IIb–IIIa glycoprotein inhibitors may be effective in prevention and treatment of no-reflow. The phenomenon of no-reflow can cause ischemia (secondary ischemia) to continue beyond the recanalization of the epicardial artery. However, reperfusion inflammation and injury are not prevented or treated in daily practice.

6. Perspectives

The development of reperfusion therapies for AMI was shown to reduce mortality strongly. There are possibilities to optimize its use. Health teams must continue fighting to shorten the system times and detect the best strategy according to the context in which they operate. There are working groups that carry out research in basic sciences, translational research, and clinical research and are making advances in myocardial protection. Cyclosporine and colchicine are currently evaluated for their ability to reduce the damage caused by inflammation. Developed treatments

for *continuing myocardial protection* [52], which the clinical cardiologists administer from the moment of diagnosis until the convalescence of the patient in a critical unit, could potentially preserve myocardium during the delay of the system and the early evolution of the event. Developed *controlled reperfusion* [52] procedures where the interventional cardiologist assumes the treatment not only of the guilty vessel but also of the myocardium could potentially decrease myocardial damage, preserve ventricular function, and improve the prognosis of patients suffering from AMI. The concept of *controlled reperfusion* involves deciding how to reperfuse (e.g., post-conditioning) and with what to reperfuse (e.g., administering to the ischemic myocardium, through dedicated catheters, before the opening of the artery, blood modified or enriched with drugs), preparing the myocardium for a more complete and definitive recovery.

A wide field of research appears to improve the treatment outcome of patients suffering from AMI aiming not only at arterial recanalization but also at myocardial preservation.

Abbreviations

AMI	acute myocardial infarction
ECG	electrocardiogram
ROS	reactive oxygen species
ADA	anterior descending artery

Author details

Miguel Angel Farah*, Franco Farah and Miguel Alejandro Farah
MEDIS Institute, Salta, Argentina

*Address all correspondence to: farahale@yahoo.com

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