Why can primary angioplastics be ineffective despite the precocity of the intervention?

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Early coronary revascularization is a first choice therapeutic strategy in the case of acute myocardial infarction (MI). Despite an early coronary angioplasty, however, in some cases, there is a lower efficacy of revascularization, with less favourable clinical outcome in the short and long terms. Various elements participate in the distant prognosis after primary coronary angioplasty (PCI). Among the clinical risk factors that predispose to a recurrence of ischaemic cardiovascular events are advanced age, diabetes mellitus, chronic renal failure, peripheral vascular disease, atrial fibrillation and the multiplicity of cardiovascular risk factors, which identify a higher baseline risk profile. The risk factors associated with the percutaneous interventional procedure include the presence of diffuse or complex coronary lesions, the use of small diameter stents or a suboptimal post procedural thrombolysis in MI flow. The occurrence of procedural complications, such as no-reflow, is in fact associated with an increase in the infarct area and a worse prognosis, as it favours negative ventricular remodelling. The presence of concomitant right ventricular dysfunction, the high ventricular arrhythmic burden in the acute phase, the presence of risk factors for thrombosis or intra-stent restenosis also affect the outcome after primary PCI.

Introduction

Early coronary revascularization is a first choice therapeutic strategy for acute STEMI. Despite early coronary angioplasty, however, in some cases, there is a lower efficacy of revascularization, with less favourable clinical outcome, both in the short and long terms. Indeed, various elements participate in the long term prognosis after primary percutaneous coronary intervention (PCI) (Figure 1). These include clinical risk factors related to patient characteristics or co-morbidities, procedural variables, and differences in clinical presentation. Factors intrinsic to the patient that can influence prognosis are age, the presence of renal failure, diabetes mellitus or poly district vasculopathy. On the other hand, the effectiveness of angioplasty also depends on the complexity of the procedure and the anatomical characteristics of coronary heart disease, as well as the clinical presentation.

Clinical risk factors

Several clinical factors have been related to an increased risk of adverse events in patients with coronary artery disease (CAD). Advanced age and in particular frailty are associated with a higher mortality. The presence of diabetes mellitus, chronic renal failure or peripheral vascular disease negatively affects prognosis, as it is more frequently associated with multivessel or diffuse CAD, as well as a more rapid progression of CAD over time. The presence of diabetes mellitus also affects a higher incidence of intrastent restenosis (ISR) during follow-up, even after the introduction of the latest generation drug eluting stents (DES) 2,3

Among the clinical risk factors associated with a higher incidence of major adverse cardiovascular events (MACE)
in the course of myocardial infarction (MI), the presence of severe left ventricular dysfunction, left bundle branch block and involvement of the anterior wall has also been described, as well as a history of previous MI and concomitant multiple cardiovascular risk factors. Finally, the onset of atrial fibrillation during acute coronary syndrome (ACS) exposes the patient to an increased risk of MACE, both in the acute and distant phases, regardless of the extent of the infarct zone, and to a greater residual impairment of the ejection fraction of the left ventricle.

In addition to the clinical characteristics of the patients, some blood markers have also been proposed for the stratification of the future risk of adverse events. The finding of increased levels of NT-proBNP during ACS, for example, correlates with a greater extent of myocardial necrosis (even in the absence of left ventricular dysfunction) and is associated with a worse prognosis, in terms of increased mortality and higher risk of ventricular systolic dysfunction. In fact, the current ESC Guidelines recommend the use of NT-proBNP as a prognostic element in the context of ACS. The extent of troponin elevation, moreover, in particular of high sensitivity troponin, is directly proportional to ischaemic damage and myocardial necrosis and correlates with a worse prognosis. Its serial evaluation is, therefore, indicated (Class I B) to stratify the risk and prognosis in ongoing MI.

**Procedural risk factors**

The introduction of second and third generation DES has made it possible to deal with progressively more and more complex coronary situations, associated with high procedural success and reduced rates of ISR, such as multi-vessel coronary lesions, stenosis of the left main coronary artery and/or bifurcations, calcified lesions, disease of tortuous coronary vessels or of completely occluded vessels (chronic total occlusion). Despite the evolution of materials and the progress of interventional cardiology techniques, however, complex percutaneous revascularizations have a lower procedural success rate and a greater recurrence of MACE during follow-up than interventions on simpler lesions. Several studies have also highlighted an increased risk of new thrombotic events in patients undergoing complex PCI.

The conditions in which angioplasty is performed and the final result can also significantly influence the outcome. In particular, patients with MI and thrombolysis in MI (TIMI) 3 flow prior to myocardial revascularization have a lower risk of mortality, heart failure and intubation than patients with reduced initial TIMI flow. The post-procedural TIMI flow affects even more markedly 30-day and long-term mortality in the case of PCI for MI. In patients with STEMI, the presence of a high thrombotic burden at the coronary level is frequent. In this context, the embolization of thrombotic material in the distal coronary segments can compromise myocardial reperfusion, with the development of necrosis despite the precocity of angioplasty and coronary recanalization. Risk factors associated with a higher incidence of significant embolization included MI in the right coronary artery and the presence of culprit lesions with a diameter >3 mm. In particular, despite an early coronary recanalization, in a variable percentage of patients, between 5 and 50% depending on the case series, there is a failure to recover coronary perfusion. This
The persistence after the acute phase of MI is predictive of post-acute outcome. Revascularization is associated with a better prognosis, especially if complete revascularization of multivessel CAD is confirmed. In the presence of no-reflow during primary PCI, associated with an increase of adverse events during follow-up. Various methods were used to quantify the outcomes and consequences of no-reflow, including the time of resolution of the ST elevation on the ECG, cardiac magnetic resonance and CT with a study of the perfusion of the microcirculation. Factors that predispose to no-reflow are diabetes mellitus, a high thrombotic burden at the level of the culprit lesion, a greater interval between onset of symptoms and PCI and a greater ischaemic area at risk (for example, in the case of heart attack due to occlusion of the proximal anterior descending). There is also an individual predisposition to no-reflow probably mediated by a greater susceptibility to coronary microcirculatory damage (favoured, for example, by comorbidities, such as diabetes mellitus and dyslipidaemia) and by hyper-activation of platelets and inflammatory mediators. It is of fundamental importance to identify patients at greater risk of no-reflow early, in order to implement appropriate preventive strategies.

A further factor that can impact on the outcome is the extent of coronary heart disease. In the presence of multivessel CAD, in fact, a higher risk of mortality and MACE is observed, especially if complete revascularization is not obtained during hospitalization for STEMI. Performing multivessel angioplasty early (within 24 h of MI diagnosis), however, is able to reduce in-hospital mortality by approximately three times (from 2.3 to 0.8% in an analysis by Kong et al.11). Finally, among the factors that can influence the prognosis after PCI for ACS, there is also the onset of early in-stent thrombosis, which, although with a low overall incidence (<2%), is more frequent in the case of primary PCI than in elective PCI, especially in the context of the use of small diameter stents, stent misapplication or incomplete plaque coverage, while the use of Gp IIb/IIa inhibitors may reduce the risk.7

Specific aspects of clinical presentation and post-acute outcome

Right ventricular dysfunction

Beyond comorbidities and coronary anatomical features or risk factors related to the revascularization procedure, the presence of concomitant right ventricular dysfunction can significantly influence the prognosis of patients with MI, even if treated with early primary PCI, associated with an increase of adverse events during follow-up. The presence on echocardiography of a reduced fractional area change and/or compromised right ventricular strain values was in particular associated with a higher total mortality rate, hospitalizations for heart failure or myocardial re-infarction.12

Negative ventricular remodelling and inflammatory state

Negative (or adverse) ventricular remodelling following MI is the result of complex myocardial cellular mechanisms, with interactions between neuro-hormonal factors and epigenetic modulation, which lead to an alteration of the structure and geometry of the heart and consequently of its function. From a microscopic point of view, the changes occur in the heart in its entirety, generally affecting not only both ventricles, but also the atrial chambers. Consequence of adverse remodelling is a reduction in cardiac contractile function, with an increase in filling pressures and an increased risk of developing heart failure. There are two types of ventricular remodelling after MI: an early one (within 2-3 weeks of the acute event) and a late one, which starts after 3-6 months. Several studies have shown that the main factor associated with an increased risk of negative remodelling is delayed coronary recanalization;11 this occurrence, however, can occur, albeit less frequently, in the case of early primary PCI. The onset of no-reflow is generally a sign of impairment of the microcirculation and significantly predisposes to the appearance of negative remodelling. Even the ‘slow-flow’ is able to favour both early and late negative remodelling.13

After primary PCI, even if it is performed early, several factors can contribute to the development of negative, usually early, ventricular remodelling: changes in vascular remodelling; delayed healing of the endothelial layer or the entire arterial wall; onset of in-stent thrombosis or ISR. A malapposition of the stent, a rupture of the mesh (actually more frequent with first generation stents) or incomplete plaque coverage are further factors which, favouring the persistence of myocardial ischaemia, can increase the risk of negative remodelling.13

With regard to late remodelling, this seems secondary above all to situations of vascular dysfunction, in particular to persistent inability to regenerate the endothelium and endothelial dysfunction, with the development of a state of chronic vasoconstriction and accelerated atherosclerosis.

In the presence of acute myocardial ischaemia and myocardial necrosis, multiple pro-inflammatory and pro-thrombotic pathways are triggered, with platelet hyper-activation.14 The persistence after the acute phase of MI of an inflammatory state, with increased levels of pro-inflammatory cytokines, negatively affects myocardial function, favouring the cellular mechanisms that lead to adverse remodelling. In fact, cytokines inhibit the vascular repair process, induce and maintain endothelial dysfunction and support the activation of platelets and the coagulation cascade, favouring episodes of recurrent ischaemia. In the months following primary PCI, the myocardial extracellular matrix is subjected to a continuous process of remodelling, in which
fibroblasts, myofibroblasts and antigen presenting cells undergo apoptosis, while the cellular debris is eliminated by macrophages. In patients undergoing PCI, mainly for ACS, platelet hyperactivation is able to influence distant mortality.  

The regulation of the cellular proliferative response and the variation of the cellular phases of tissue inflammation are mainly mediated by the renin-angiotensin-aldosterone system and the orthosympathetic system. Furthermore, the adrenergic system also plays a fundamental role in maintaining the post-MI inflammatory state. The persistence and hyperactivation of these mechanisms predispose to negative cardiac remodelling, even in the case of primary PCI performed early. Therapy with ACE inhibitors and beta-blockers, by inhibiting these mechanisms, has been associated with an improvement in ventricular remodelling. Failure to take (or poor titration) of these drugs, therefore, represents an additional factor capable of favouring the development of adverse remodelling.

**Intrastent restenosis**

Despite the use of the latest generation of DES, in a non-negligible percentage of patients, varying between 2 and 10%, ISR can occur after PCI. The appearance of ISR increases mortality and morbidity after PCI. It is estimated that about 5-10% of MI occurs in correlation with ISR phenomena. During PCI, vessel baro-trauma occurs, resulting in endothelial and vascular damage, and activation of the inflammatory response. Endothelial damage and inflammation trigger the proliferation and migration of smooth muscle cells and fibroblasts and the creation of neo-intimal tissue, which, in the event of excessive hyperplasia, can cause ISR. The degree of neo-intimal hyperplasia correlates with the extent of vascular damage. Furthermore, the reduction in blood flow causes local activation of coagulation and the formation of fibrin clots, which, in turn, promote the migration of macrophages. The release of anti-proliferating agents by DES counteracts these phenomena and reduces the incidence of ISR compared with non-medicated stents.

The risk of ISR, even early, increases in the case of complex coronary lesions (bifurcations and total occlusions), calcified stenosis, reduced vascular calibre, lesions with a length >20 mm and incomplete expansion of the stent. An increased incidence of ISR is observed in diabetic patients, hypertensive, with previous coronary bypass or episodes of heart failure in their history.

**Arrhythmic burden**

The presence of ventricular arrhythmias is common in the context of ACS. An increased risk of mortality (both 30 days and distant) and intrastent thrombosis within 3 years was observed in patients with ventricular tachycardia and/or ventricular fibrillation before coronary revascularization for ACS. Risk factors associated with an increased incidence of sustained ventricular arrhythmias are presence of STEMI (vs. non-STEMI), short interval between onset of symptoms and access to treatment, arterial hypertension, obstructive bronchopathy, previous MI or dynamic changes in the ST segment. Early initiation of beta-blocker therapy reduces the risk of sustained ventricular arrhythmias in patients with MI. A protective role of eicosapentaenoic acid administered in the acute phase of MI has also been hypothesized, in terms of reducing the inflammatory state and decreasing the onset of ventricular arrhythmias.

**Score for risk stratification**

Some scores have been created for the stratification of clinical risk in patients with STEMI, such as GRACE (Global Registry of Acute Coronary Events) and TIMI, which represent the most validated and used scores in clinical practice. By using different parameters, different risk profiles of MACE at follow-up were thus drawn up, based on the patient’s clinical and procedural characteristics. The TIMI risk score includes eight factors (assigned a certain score) to define the risk of in-hospital mortality in the presence of STEMI: age ≥75 years or between 65 and 74 years, history of diabetes mellitus, arterial hypertension or angina, systolic blood pressure <100 mmHg, Killip Class III and IV, weight <67 kg, ST segment elevation in anterior leads or left bundle branch, reperfusion time >4 h. A score of 0 is associated with a 30-day mortality of 0.8%, while a score ≥8 points correlates with a mortality of 36%. Data from the TIMI-III registry also allowed to stratify the risk of adverse events or death at 1 year on the basis of electrocardiographic aspects at admission: the highest rate of MACE was observed in patients with left bundle branch block at entry (15.8%), followed by patients with changes of the ST segment of at least 0.5 mm and alterations on the anterior leads.

The GRACE study, with data collected in 14 countries for a total of >17,000 patients, allowed to draw up the GRACE score, which identifies the risk of MACE at 6 months (and at 3 years in the case of GRACE 2.0) in the presence of ACS (both non-STEMI and STEMI). The score is composed of nine variables (age, heart rate and blood pressure at admission, serum creatinine, history of MI or heart failure, ST-segment abnormalities, increased myocardial necrosis markers at admission and absence of PCI during hospitalization) and has been extensively validated in several studies.

More recently, the score derived from the Acute Coronary Treatment and Intervention Outcomes Network registry has been proposed to predict mortality in patients with STEMI (or non-STEMI) on >243,000 patients. This score identified high heart rate, hypertension, clinical presentation with cardiac arrest/ cardiogenic shock/heart failure, presence of STEMI (vs. non-NSTEMI), decreased creatinine clearance and elevated troponin values as predictors of in-hospital death (C-statistic equal to 0.88).

Moreover, other scores including procedure-related parameters to identify patients with MI at increased risk for future adverse events were also created. The Zwolle score is based on the Killip class at admission, the presence of three-vessel CAD, the post-procedure
TIMI flow, age, the presence of anterior wall alterations and the ischaemic time (>4 h) to define the risk of in-hospital and 30-day mortality, as well as ventricular arrhythmic burden. A low Zwolle score (≤3 points) was associated with a very low incidence of mortality (0.5% at 30 days) and malignant ventricular arrhythmias (0.2% risk of ventricular tachycardia/ventricular fibrillation at 48 h), allowing for stratification lower-risk patients able to benefit from early discharge. Finally, the CADILLAC score identified left ventricular ejection fraction at baseline as the most potent predictor of MACE at 12 months, followed by a suboptimal post-procedure TIMI flow.6

Conclusions

The short and long-term outcome after primary angioplasty depends in the individual patient on a multiplicity of factors related to comorbidities, the extent of the atherosclerotic disease, the complexity of coronary revascularization, the onset of any early complications (no-reflow, thrombosis acute/subacute, early ISR), in the inflammatory and pro-thrombotic state and in early and late ventricular remodelling. These factors can influence prognosis even in early primary PCI. Risk stratification makes it possible to identify the best therapeutic options in the individual patient to reduce the risk of adverse events as much as possible, even after early primary PCI.

Conflict of interest: None declared.

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