Strategies to prevent left ventricular remodeling

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Conflicts of interest: None.

Left ventricular maladaptive remodeling after ST-segment elevation myocardial infarction (STEMI) has been consistently associated with an increased incidence of congestive heart failure and impaired prognosis [1,2]. Among other factors such as anterior localization and quality of collateral circulation, infarct size is one of the major predictors of left ventricular remodeling. Once the myocardial damage has been established, pharmacological or device-based treatments are intended to treat, prevent, or slow the progression towards the heart failure syndrome (''secondary'' prevention). However, the most effective treatment strategy with a recognized significant impact on the prognosis of patients with STEMI is ''primary'' prevention through limitation of infarct size [3].

Final infarct size is dependent on two major determinants: total ischemic time and reperfusion-related myocardial damage. Experimental models of coronary occlusion have shown that a large fraction of the myocardium at risk remains viable when reperfusion occurs within 30–60 min, with the percentage of salvageable myocardium rapidly decreasing beyond the first 1 h of ischemia [4]. On the basis of this evidence, prompt reperfusion, either mechanical or pharmacological, is recognized as the optimal treatment strategy for the management of patients with STEMI in all recent guidelines, which strong recommend 30-min door-to-needle and 90-min door-to-balloon times [5]. Time delays have been identified as the central point in the decision-making process concerning the best treatment strategy, superiority of primary percutaneous coronary intervention (PCI) over fibrinolysis having been demonstrated only in so far as the time to reperfusion is not exceedingly increased by opting for PCI. However, despite considerable progress in myocardial reperfusion strategies achieved over the past 20 years, the in-hospital rate of death for acute myocardial infarction in the ''real world'' still approaches 10%, and the incidence of subsequent cardiac failure is almost 25%. Registry data show that the established goals for total ischemic time are extremely difficult to achieve. In particular, door-to-balloon times are often much longer than reported in randomized clinical trials because, in the ''real world'', transfer of patients for PCI, local factors (ie, geographic location), and poor management strategies lead to longer delays [6]. In the National Registry of Myocardial Infarction, only 4.2% of patients undergoing primary PCI achieved a door-to-balloon time less than 90 min [7]. Moreover, up to one-third of patients eligible for fibrinolytic therapy did not receive effective early reperfusion because of factors such as late presentation or lack of efficacy of thrombolytic agents [8].

The current challenge is therefore the implementation of protocols capable of reducing the time between symptom presentation and effective reperfusion (total ischemic time). Possible strategies could include, for example: educating patients to be prompt in the recognition of symptoms and in alerting the emergency services; transmission of the electrocardiogram recorded in the field; bypassing the emergency room. Nonetheless, rapid restoration of coronary flow does not always result in myocardial salvage and consistently guarantee a reduction in the infarct size. In about one-third of patients, myocardial reperfusion is followed by microvascular damage resulting in the so-called no-reflow phenomenon, as originally described by Kloner et al [9]. This phenomenon is associated with a sevenfold increase in mortality (from 0.7% to 5.4%) and heart failure [10–12].

The capillary structure is damaged by ischemia, with tissue compression, myocyte edema, and neutrophil infiltration [13]. This pathologic process can be accentuated by coronary reperfusion, leading to progressive decline in coronary flow [14]. In this way, reperfusion has the potential to add to the damage produced by the ischemic insult, thereby offsetting the beneficial effects of flow restoration. Studies of AMI in animal models suggest that lethal reperfusion injury, which starts immediately after the opening of the culprit coronary artery, accounts for up to 50% of the final infarct size [15]. Thus reperfusion injury should be regarded as a major therapeutic target in patients with STEMI.

Hot topics

Several strategies have been shown to reduce reperfusion injury in animal models, including administration of cardioprotective agents (eg, adenosine, cariporide, metabolic agents, calcium channel blockers), mechanical prevention of distal coronary embolization, intermittent reperfusion (postconditioning), and thrombus aspiration. Unfortunately, translation to the clinical setting has not yielded consistent benefits.

The negative results of most clinical trials addressing ischemia-reperfusion injury have led us to question the clinical relevance of reperfusion injury. Several confounding factors should be taken into consideration when discussing the effects of cardioprotective agents. First, difficulties in reproducing the human disease in animal models. Secondly, variability in the route of administration of the cardioprotective agents (intravenous administration of adenosine in the Acute Myocardial Infarction Study of Adenosine [AMISTAD] II trial). Thirdly, but not least, a lack of a predefined and homogenous duration of ischemia before the initiation of treatment. The clinical impact of reperfusion injury may be negligible when reperfusion is achieved after several hours of ischemia, when all myocardium at risk is irreversibly damaged. Conversely, reperfusion damage may be much more relevant when the vessel is reopened early and a sizeable part of viable myocardium is still present.

At present, there are two strategies that have been shown to limit reperfusion injury in the setting of AMI: postconditioning and intracoronary administration of adenosine. Brief episodes of ischemia, at the time of reperfusion, have been reported to reduce infarct size dramatically [16–18]. Similarly, intracoronary adenosine, as an adjunct to primary percutaneous transluminal coronary angioplasty, has been shown to ameliorate flow, prevent the no-reflow phenomenon, improve ventricular function, and to be associated with a more favorable clinical course [19]. Thrombectomy, which improves surrogate endpoints, does not affect 30-day mortality, reinfarction, and stroke, according to the findings of a recent meta analysis [20].

In conclusion, timely reperfusion of the infarct-related artery and effective cardioprotection must be combined to limit infarct size and prevent left ventricular remodeling. ■

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