JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 65, NO. 14, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.02.032

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Evolving Therapies for Myocardial Ischemia/Reperfusion Injury

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CME Objective for This Article: After reading this article, the reader should be able to: 1) relate the importance of infarct size (amount of myocardium irreversibly injured during an ST-segment elevation acute myocardial infarction [STEMI]), and the need to find novel/better therapies able to reduce infarct size; 2) discuss the difference between ischemic and reperfusion injuries; 3) acknowledge that, on the basis of a timely reperfusion, additional interventions/therapies are needed to reduce the impact of reperfusion injury and, ultimately, infarct size; 4) discuss the global general pathways implicated in reperfusion-mediated injury; and 5) describe the main interventions holding the potential to reduce ischemia/reperfusion injury.

CME Editor Disclosure: *JACC* CME Editor Ragavendra Baliga, MD, FACC, has reported that he has no financial relationships or interests to disclose.

Author Disclosures: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval

Issue Date: April 14, 2015
Expiration Date: April 13, 2016

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Manuscript received February 19, 2015; accepted February 22, 2015.

Evolving Therapies for Myocardial Ischemia/Reperfusion Injury

ABSTRACT

The damage inflicted on the myocardium during acute myocardial infarction is the result of 2 processes: ischemia and subsequent reperfusion (ischemia/reperfusion injury). During the last 3 decades, therapies to reduce ischemic injury (mainly reperfusion strategies) have been widely incorporated into clinical practice. The remarkable reduction in death rates achieved with these therapies has resulted in a shift in emphasis from efforts to reduce mortality to a focus on tackling the downstream consequence of survival: post-infarction heart failure. Infarct size is the main determinant of long-term mortality and chronic heart failure, and thus, the possibility of limiting the extent of necrosis during an ST-segment elevation myocardial infarction is of great individual and socioeconomic value. After the great success of therapies to reduce ischemic injury, the time has come to focus efforts on therapies to reduce reperfusion injury, but in the recent few years, few interventions have successfully passed the proof-of-concept stage. In this review, we examine the past, present, and future therapies to reduce ischemia/reperfusion injury. (J Am Coll Cardiol 2015;65:1454–71)

Acute myocardial infarction presenting as ST-segment elevation (STEMI) is the result of abrupt occlusion of an epicardial coronary artery. As a result, the myocardium distal to the occlusion site becomes ischemic. Unrelieved ischemia causes permanent damage to the myocardium previously supplied by the occluded artery. Myocardium is destroyed and replaced by fibrous scar tissue. Because scar tissue does not contribute to myocardial contractile function, if the scar is large, global left ventricular (LV) contractile function is impaired, resulting in progressive chronic heart failure. After the demonstration that coronary thrombosis was the cause (not the result) of STEMI in the vast majority of cases, timely restoration of blood flow to the ischemic myocardium (reperfusion) became the standard treatment for these patients. Reperfusion was rapidly demonstrated to limit infarct size, improve long-term myocardial function, change the healing pattern of the infarcted zone, and more importantly, reduce mortality. A large body of experimental and clinical evidence supports the notion that reperfusion induces additional damage to the myocardium, known as reperfusion injury. As a result, the damage inflicted on the myocardium during an STEMI is better defined as *ischemia/reperfusion (I/R) injury*, the result of ischemic and reperfusion processes. Myocardial I/R injury is a complex phenomenon involving many players, all contributing to the final damage inflicted on the heart (**Central Illustration**).

In the present review, we describe the evolving therapies for the treatment of myocardial I/R injury. These include therapies targeting both ischemic and reperfusion damage. To explain the rationale for the quest for new and better therapies, we describe the pathophysiology of myocardial I/R injury and the translational path of research, from the pre-clinical discovery phase, through proof-of-concept clinical trials, to large trials aimed at changing clinical practice. In the context of this paper, the term myocardial infarction always refers to STEMI.

IMPACT OF STEMI IN 2015: A PARADIGM SHIFT

The incidence of STEMI in Western countries has declined during the last decades due to the progressive implementation of preventive therapies and better control of risk factors (1). Despite the progressive and gradual decrease in its incidence, STEMI remains a significant health problem, representing a major contributor to mortality/morbidity worldwide (1). As detailed later in this review, the implementation of timely reperfusion has resulted in a very significant reduction in the acute mortality associated with STEMI. Risk-adjusted in-hospital mortality has decreased from ≈20% in the late 1980s to ≈5% among STEMI patients treated in routine practice in 2008 (2), reaching a plateau thereafter (3). However, these impressive reductions in mortality rates, resulting from the widespread use of reperfusion strategies and adjuvant pharmacological therapies, have resulted in an increase in the incidence of chronic heart failure. Although this outcome might at first seem paradoxical, the explanation is simple: patients with a severely depressed cardiac function would not have survived