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Update: Acute Coronary Syndromes (IV)

Protection Against Myocardial Ischemia-reperfusion Injury in Clinical Practice

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ABSTRACT

Even when reperfusion therapy is applied as early as possible, survival and quality of life are compromised in a considerable number of patients with ST-segment elevation acute myocardial infarction. Some cell death following transient coronary occlusion occurs during reperfusion, due to poor handling of calcium in the sarcoplasmic reticulum-mitochondria system, calpain activation, oxidative stress, and mitochondrial failure, all promoted by rapid normalization of intracellular pH. Various clinical trials have shown that infarct size can be limited by nonpharmacological strategies—such as ischemic postconditioning and remote ischemic conditioning—or by drugs—such as cyclosporine, insulin, glucagon-like peptide-1 agonists, beta-blockers, or stimulation of cyclic guanosine monophosphate synthesis. However, some clinical studies have yielded negative results, largely due to a lack of consistent preclinical data or a poor design, especially delayed administration. Large-scale clinical trials are therefore necessary, particularly those with primary clinical variables and combined therapies that consider age, sex, and comorbidities, to convert protection against reperfusion injury into a standard treatment for patients with ST-segment elevation acute myocardial infarction.
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Protección contra el daño miocárdico por isquemia-reperfusión en la práctica clínica

Palabras clave:
Daño por reperfusión
Infarto de miocardio
Condicionamiento isquémico remoto
Proteicinasa G

RESUMEN

Pese a recibir lo más tempranamente posible la terapia de reperfusión, un amplio número de los pacientes que sufren infarto agudo de miocardio con elevación del segmento ST tienen infartos que comprometen su supervivencia y su calidad de vida. Parte de la muerte celular secundaria a una oclusión coronaria transitoria ocurre durante la reperfusión, por mal manejo del calcio en el sistema retículo sarcoplasmático-mitocondria, activación de calpaínas, estrés oxidativo y fallo mitocondrial, favorecidos por la rápida normalización del pH intracelular. Varios ensayos clínicos han demostrado que se puede limitar el tamaño del infarto mediante estrategias no farmacológicas —como el poscondicionamiento isquémico y el condicionamiento isquémico remoto— o farmacológicas —como la estimulación de la síntesis de guanosina monofosfato cíclico, la insulina, los agonistas del péptido glucagonoide tipo 1, los bloqueadores beta o la ciclosporina. Diversos ensayos clínicos han dado resultados negativos, en la mayoría de los casos por falta de datos preclínicos consistentes o un diseño equivocado, en particular, administración tardía. Son necesarios, pues, ensayos clínicos grandes con variables clínicas primarias y terapias combinadas y que consideren edad, sexo y comorbilidades, para que la protección contra el daño por reperfusión se convierta en un tratamiento estándar para los pacientes con infarto agudo de miocardio con elevación del segmento ST.
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INTRODUCTION

Importance of the Problem. Contribution of Cell Death to the Social Impact of Ischemic Heart Disease

Ischemic heart disease is the leading cause of death worldwide and, unless previous trends are modified, will continue to be the most common cause of death in 2030.[1] The social impact of ischemic heart disease is considerable, not only because of the mortality it causes, but also because of its consequent morbidity, loss of quality of life, and high economic cost. This impact is largely due to a pathophysiological mechanism, namely, cardiomyocyte death. In ischemic heart disease, cardiomyocyte death almost always occurs in the context of severe and prolonged myocardial ischemic events, which are a consequence of thrombotic complications from atherosclerotic plaques in epicardial coronary arteries, known as acute coronary syndrome. Cardiomyocyte death is more significant when ischemia is caused by complete coronary occlusion, lacks well-developed collateral circulation, affects the majority of the left ventricular wall thickness, and shows ST-segment elevation on an electrocardiogram (ST-segment elevation acute myocardial infarction [STEMI]).

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Abbreviations

mPTP: mitochondrial permeability transition pore
PKG: protein kinase G
PostC: postconditioning
RIC: remote ischemic conditioning
STEMI: ST-segment elevation acute myocardial infarction

The cell death that occurs in acute coronary syndrome not only causes a direct loss of contractile activity, but can also cause geometric changes in the infarcted wall and adaptive changes in the remaining myocardium, which ultimately lead to general dysfunction and dilatation of the ventricle, a process called adverse remodeling.[2,3] Scarring and adverse remodeling cause heart failure and promote the appearance of potentially fatal ventricular arrhythmias,[4] so that cell death occurring during acute coronary syndrome eventually determines not only acute-phase mortality, but also long-time morbidity and mortality.[5]

Accordingly, reducing cell death during acute coronary syndrome, and in particular during STEMI, appears to be an obvious strategy for reducing the impact of ischemic heart disease on health and society.

Prevention of Reperfusion Injury as a Strategy to Reduce the Impact of Ischemic Heart Disease

Ischemic heart disease has mixed genetic and environmental etiology whose pathological substrate is the atherosclerotic plaque. Coronary atherosclerosis develops in a clinically silent manner over years and only causes clinical symptoms when the vessel lumen is greatly narrowed, either due to atherosclerotic plaque growth or the development of intracoronary thrombosis due to plaque complication, resulting in a loss of endothelial continuity due to erosion, fissure, or endothelial rupture.[6] Thus, preventing the appearance of atherosclerosis coronary plaques or their progression is the first line of action against the disease.

Prevention of ischemic heart disease is not without difficulties. Population-wide interventions are expensive and cannot be particularly aggressive due to the risk of costly adverse events. The more aggressive interventions—aimed at avoiding plaque growth, reducing the risk of complications, or attenuating secondary thrombosis—should be limited to those individuals at high risk of the disease. Although much progress has been made in identifying risk factors and developing methods to calculate individual risk,[7] conventional risk factors for the disease are poorly controlled.[8] Moreover, genetic studies have identified multiple loci associated with the development of atherosclerosis disease, but this association is weak and its effect on the predictive value of conventional risk factors is limited, particularly when family history is taken into account. The difficulty in preventing ischemic heart disease is clear upon observing changes in its incidence in specific populations. Spain, for example, is far from controlling ischemic heart disease through preventive measures, given that the incidence of conventional risk factors has largely been stable and in some cases is predicted to increase, as is happening with type 2 diabetes mellitus, which has proliferated due to the growth in childhood obesity.[9,10]

The effectiveness of risk stratification and prevention strategies should be measured not only by their ability to reduce the appearance of clinical symptoms of ischemic heart disease, but more specifically by their ability to reduce the incidence of acute coronary syndrome and, in particular, acute myocardial infarction (AMI), which causes most of the morbidity and mortality associated with the disease. However, extensive evidence indicates that it is difficult to predict the occurrence of AMI. In a recent large study, performed in 542 008 patients with a first myocardial infarction, approximately half had only one risk factor or none at all.[11,12] Moreover, analysis of distinct patient subgroups revealed that in-hospital mortality was inversely proportional to the number of classical risk factors present.[11] Taking both observations together, it can be estimated that most patients that die in hospital from their first AMI show a low risk profile, with 0-1 risk factors. Accordingly, although efforts to improve risk stratification and prevention of ischemic heart disease are clearly essential, no less essential is the need to improve the effectiveness of AMI treatment to improve prognosis. In many cases, this approach is the first and only option available to alter the course of the disease.

The prognosis of AMI largely depends on its extent, that is, the number of cells that die during the event.[13] The final necrotic extent is mostly due to the speed of the progression of ischemic injury (influenced by residual blood flow, whether through the lesion or through collateral circulation, and by temperature, among other factors) and the duration of the ischemia.[14,15] The most effective treatment to limit infarct size is early reperfusion.[16–18] However, the amount of myocardium salvaged by reperfusion rapidly decreases the longer it is delayed, and the window in which reperfusion effectively limits infarct size in patients with STEMI is short. After 3 h of ischemia, without collateral circulation and residual flow (TIMI [Thrombolysis in Myocardial Infarction] 0), the amount of salvaged myocardium is typically small or nonexistent.[19] Nonetheless, late reperfusion is also beneficial, and should generally be performed within 12 h of symptom onset.[20] In this case, however, the benefit is due to the positive effects of reperfusion on healing, with reperfusion limiting infarct expansion and secondary adverse remodeling (Figure 1).[20]

Because of the short reperfusion window for limiting infarct size, necrosis affecting most of the ventricular wall thickness-causing Q-waves and worsening prognosis-cannot be prevented in most patients, despite the availability of systems of rapid administration of reperfusion treatment (such as primary angioplasty or thrombolysis without emergency department referral, and optimal antiplatet and anticoagulant agents, etc. The conventional outlook is that when patients with STEMI arrive at the catheterization laboratory, as it is no longer possible to reduce the ischemia duration or modify the collateral circulation or residual coronary flow (TIMI flow), the only remaining approach is to open the artery as much as possible and see if patients have arrived in time to save the myocardium. However, a wealth of preclinical information and a growing amount of clinical data indicate that the proportion of reperfusion-salvaged myocardium can be increased by applying treatments more or less at the time of reperfusion. The present article examines the current situation and the expected future of treatments aimed at reducing cell death in patients with STEMI that receive reperfusion treatment, and will not therefore analyze the effectiveness of these treatments in other clinical contexts, such as cardiac surgery or cardiopulmonary resuscitation.

REPERFUSION INJURY

Concept

The first laboratory experiments with transient coronary occlusion showed a paradoxical worsening during reperfusion of the functional changes associated with ischemia, particularly arrhythmias.[21–23] Studies in isolated and perfused hearts revealed an increase in cardiac enzyme release upon reperfusion following a

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