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Myocardial Ischemia – A Pathophysiology and Management Methods

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Abstract

Myocardial ischemia is considered the cornerstone of the treatment of patients with coronary artery disease (CAD). Although the deleterious effects of myocardial infarction, the maximum expression of ischemia, have been extensively studied and described, the clinical effects of chronic, documented myocardial ischemia are not completely clarified. The first studies that compared therapies for coronary disease focused on the presence of anatomical features and assessed ischemia based on the interpretation of the findings of obstructive atherosclerotic lesions. They suggested that revascularization interventions did not confer any clinical advantage over medical therapy (MT), in terms of cardiac or overall death. Other retrospective studies that were dedicated to assessing the impact of documented stress-induced ischemia on cardiovascular outcomes have suggested a prognostic impact of chronic ischemia.

Keywords: Myocardial infarction; ischemia; myocardium; atherosclerosis; myocardium

Introduction

Translating single, mechanistic basic experimental research to clinically beneficial outcomes is not a parallel, idealized process. Predicting clinically meaningful outcome endpoints is difficult, even from a well-recognized, robust preclinical indicator. The contradiction between successful animal research and ineffective translation of clinical effects has become an urgent problem to be solved. Due to improved tertiary prevention strategies, mortality in ST-segment elevation myocardial infarction (MI) patients has declined over the past 15–20 years, while the number of patients with post-MI heart failure is increasing. The unpredictable onset of acute MI severely limits pharmacologically protective preconditioning. However, this does not mean that cardio protection is no longer necessary. It is just that it is increasingly difficult to demonstrate its utility, so the target population must be carefully selected. There is still, and always will be, a subset of patients who develop heart failure, especially those with the anterior wall or multiple recurrent MI. This may be why cardioprotective research is still ongoing for 50 years. In 2019, the COST ACTION cardio protection consortium proposed a multi-target treatment strategy, that is, in the case of the coexistence of clinically uncontrollable variables, the rational combination of two or more different protection strategies may help produce a solid and robust cardioprotective effect. In this regard, we should start from the following aspects in the future to improve the possibility of successful clinical translation: (1) to deeply explore the complex pathophysiological mechanism of myocardial ischemia-reperfusion injury (IRI) and focus on the changes of the pathophysiological mechanism under the condition of comorbidities (2) clarify the classification of specific therapeutic targets and screen out more reasonable and promising multi-target therapeutic strategies based on this; and (3) establish more reliable preclinical evaluation standards and preclinical animal models that conform to clinical practice, including animal models with multiple comorbidities and animal models receiving “background drug treatment.” In addition, the multi-target therapeutic strategies that have been screened should be able to be reproduced.

The impact of multiple mechanisms of ischemia on diagnostic approaches

Current management is focused on the “epicardial coronary obstruction-first” approach, assuming that obstructive atherosclerosis remains the primary and proximate cause of myocardial ischemia, and that, in the presence of obstructive atherosclerosis, there is no need to search for other possible alternative or coexisting mechanisms of ischemia.

The Centers for Disease Control and Prevention analyzed the 50% reduction in coronary heart disease mortality between 1980 and 2000. They reported that 44% of this reduction could be attributed to improvements in population risk factors (hypertension, smoking, and hypercholesterolemia), and an additional 12% could be attributed to improved primary treatment of these risk factors.

In the American College of Cardiology National Cardiovascular Data Registry, only half the patients with a positive test had a stenosis >50% at angiography. Similarly, in the CONFIRM Registry, the prevalence of stenoses >50% was 50% in male patients, and 30% in female patients, with lower figures in younger subjects. In a large registry of 375,886 patients with stable angina pectoris, 51% of women and 33% of men had no hemodynamically significant coronary stenosis.

Sensitivity and specificity of provocative tests

The complex and dynamic nature of myocardial ischemia needs to be further underscored. Pathophysiologic mechanisms interact through intricate feedback pathways and probably in a patient-specific manner. For instance, microvascular dysfunction and inflammation may interact in some, but not all patients. Similarly, the effect of endothelial dysfunction on the coronary microcirculation is likely to be complex and variable according to sex, while coronary spasm is likely to be modulated by endothelial function, inflammation and components of the cytoskeleton.

Cardioprotective targets for myocardial IRI: Classification by ultimate protection of cellular target

Finally, cardioprotective strategies may protect cardiomyocytes or non-cardiomyocytes such as leukocytes, monocytes, macrophages, platelets, etc. Although cardiomyocytes are most susceptible to IRI, non-cardiomyocytes, including smooth muscle cells, nerve cells, endothelial cells, and fibroblasts, are also greatly affected. Other components, including extracellular vesicles, cytokines, chemokines, etc., play signal transduction functions during IRI.

Conclusion

Abnormal endothelial and VSMC functions impair coronary circulation and cause myocardial ischemia, not only in epicardial coronary arteries, but also in coronary microcirculation. Rho-kinase pathway is recognized as an important regulator of vascular function at both epicardial and microvascular coronary level and therefore emerges as a novel therapeutic target in cardiovascular medicine.

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