Inflammatory-reparative response (IRR) in hypoxic cardiomyocytes in humans and in animal models
M.A. Russo

Dept. of Experimental Medicine, Sapienza University of Rome, Italy

Acute and chronic hypoxia is a major cause of myocardial damage. Typically it occurs in myocardial infarction, diabetic cardiomyopathy, hypertrophic cardiomyopathy and storage cardiomyopathy.

Myocardial ischemia is responsible for the necrotic death of cardiomyocytes which release damage signals represented by molecules, such as HMGB1, ATP/ADP, lipids, nucleic acids, etc., also known as alarmins. These molecules bind to their receptors belonging to specific classes: a)-Receptors for advanced glycosylated end-products (RAGE) which bind HMGB1 and AGEs; b)-Purinergic receptor P2X7 which binds ATP/ADP and other nucleotides; c)-PSR receptor for phosphatydil-serine of the inner layer membrane, and d)-Toll-like receptors, binding different chemical patterns on the surface of pathogens and nucleic acids.

It is well known that the activation of such receptors in leukocytes triggers a specific gene expression NF-kB-dependent, that is responsible for the inflammatory reparative response (IRR). Leukocytes can be activated either by hypoxic necrosis through alarmin receptors, or by pathogens through pattern recognition receptors (Toll-like receptors).

Preliminary results show that in isolated cardiomyocytes the early response to hypoxia is very similar to that seen in leukocytes: activation of transcription factor HIF-1α which, in turn, transcribes the genes coding for the alarmin receptors, followed by NFkB and IRR gene activation. Other preliminary results obtained from human myocardial biopsies, in the absence of a leukocyte infiltrate, have shown that, in the reparative area of the infarction, surviving cardiomyocytes can express IRR genes, likely contributing to the post-infarctual remodelling.

It is not known whether reoxygenation (reperfusion) facilitate or inhibits the cardiomyocyte IRR phenotype.

E-mail address: matteoantonio.russo@uniroma1.it

Role of HO-1 pharmacological over-expression in modulating ischemic myocardial damage in a rat model of myocardial infarction
C. Kusmic 1, M. Matteucci 2, N. Vesentini 1, C. Barsanti 2, N. Abraham 3, L’Abbate A. 1,2

1 Istituto di Fisiologia Clinica, CNR, Pisa, Italy
2 Scuola Superiore Sant’Anna, Pisa, Italy
3 New York Medical College, USA

The occlusion of a coronary artery blocks blood flow supply to the downstream myocardium causing its metabolic derangement and the immediate loss of its contractile function. This phenomenon can be reversed by prompt restoration of perfusion (ischemia). A long lasting blood flow interruption produces an irreversible myocardial damage with tissue necrosis (infarction) and its successive substitution with scar (1-2). However, also ischemia can lead to necrosis, although of less extent, secondary to return of blood flow (reperfusion) rather than to prolonged lack of flow (3-4). Following the acute coronary event, the residual viable myocardium from one side and the infarcted segment from the other undergo profound changes in ventricular shape and geometry (remodeling) leading to a progressive loss in mechanical efficiency up to heart failure (5).

Although both the size of the occluded vessel and the duration of occlusion are crucial elements in determining the amount of myocardial loss, other factors such as vascular constriction of the coronary microvasculature, oxidative stress, inflammation, apoptosis and myocyte hypertrophy might acutely and chronically affect both infarct size and ventricular remodeling (6-8). Hemeoxygenases are a complex system that regulates the vascular tone and the modulation of oxidative stress and of cellular death by apoptosis (9-10). The two isoforms HO-1 and HO-2 are cytoprotective enzymes that breaks down the heme (a powerful oxidant), thereby generating carbon monoxide (CO, a gas with vasodilation activity and anti-inflammatory properties) bilirubin (an antioxidant compound derived from biliverdin) and iron (isolated from ferritin). The HO-2 isomorph is constitutive in the tissues, while HO-1 is induced by its substrate, free heme, as well as by oxidative stress. Goal of our study was the assessment of the effect of the pharmacologically-induced overexpression of HO-1 during the acute event, on ischemic damage and on ventricular remodelling due to ischemia-reperfusion and/or myocardial infarction in a rat model. The selected model of ischemic myocardial damage was the permanent or transitory occlusion of the descendant anterior coronary artery (LAD) since it represents the range of different clinical presentations and the polymorphism of anatomo-functional patterns of organ damage typical of acute coronary syndromes. The increase expression of HO-1 in the two animal models of myocardial damage was pharmacologically induced by cobalt protoporphyrin (CoPP) administration 10 min following LAD occlusion thus mimicking the clinical time-course of pharmacological intervention in patients presenting at the emergency room with chest pain and signs of acute myocardial ischemia. Thereafter CoPP was administered i.p. at the same dose once a week for 4 weeks. Preliminary results are in keep with the expectations regarding both the acute and chronic evidences after four weeks from LAD ligation. In addition, electrocardiografic, echocardiographic and bio-humoral data obtained in vivo as well as macro- and microscopic morphometric analysis appear to be adequate systems for a satisfactory characterization of a myocardial damage to challenge against the working hypothesis which attributes to an increase in expression of HO-1, obtained by administration of CoPP, the capability of reducing myocardial damage and ventricular remodeling.