Inflammatory-reparative response (IRR) in hypoxic cardiomyocytes in humans and in animal models

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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 myocardocytes 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 myocardocytes 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.

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Role of HO-1 pharmacological over-expression in modulating ischemic myocardial damage in a rat model of myocardial infarction

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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 vasocstriction 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 vasodilatation activity and anti-inflammatory properties) bilirubin (an antioxidant compound derived from biliverdin) and iron (isolated from ferritin). The HO-2 isoform 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 remodeling 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, electrocardiographic, 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.
Coronary microvascular function and myocardial metabolism in the pig model of pacing induced progressive LV dysfunction

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Dilated cardiomyopathy (DCM) is the third cause of chronic heart failure (HF) and is characterized by progressive ventricular dilation and functional impairment in the absence of coronary lesions and/or hypertension. Pacing-induced heart failure mimics many of the pathophysiological and molecular features of clinical non-ischemic dilated cardiomyopathy and is well-suited to perform combined in vivo and ex-vivo measurements and assays. The precise mechanisms responsible for the contractile dysfunction of idiopathic DCM are still not well defined. Research to date has mainly focused on 1) myocardial energy depletion and impaired energy substrate utilization; 2) myocardial ischemia. However, it is still debated whether these mechanisms are related to coronary microvascular dysfunction and/or mechanical dysynchrony. Increased glucose utilization and regional differences in contractile/perfusion function are well-known alterations of the failing heart and play an important pathophysiological role. We tested whether, similar to functional derangement, changes in glucose uptake develop following a regional pattern.

Chronic HF was induced in 13 chronically instrumented mini-pigs by pacing the left ventricular (LV) free wall at 180 beats/min for 3 weeks. Regional changes in LV myocardial contractility, perfusion and stress were assessed by magnetic resonance imaging, whereas regional flow and glucose uptake were measured by positron emission tomography utilizing, respectively, the radiotracers [13N]ammonia and 18F-deoxyglucose. In heart failure, LV end-diastolic pressure was 20±4 mmHg, and ejection fraction was 35±4% (all P<0.05 vs. control). Sustained pacing-induced dysynchronous LV activation caused a more pronounced decrease in LV systolic thickening (7.45±3.42 vs. 30.62±8.73%, P<0.05) and circumferential shortening (-4.62±1.0 vs. -7.33±1.2%, P<0.05) in the anterior/ventricular region (pacing site) compared with the inferoseptal region (opposite site). Conversely, flow was reduced significantly by ±32% compared with control and was lower in the opposite site region. Despite these nonhomogeneous alterations, regional endystolic wall stress was uniformly increased by 60% in the failing LV. Similar to wall stress, glucose uptake markedly increased vs. control (0.24±0.004 vs. 0.07±0.01 μmol.min⁻¹.g⁻¹, P<0.05), with no significant regional differences. In conclusion, high-frequency pacing of the LV free wall causes a dysynchronous pattern of contraction that leads to progressive cardiac failure with a marked mismatch between increased glucose uptake and regional contractile and flow dysfunction.

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Coronary microvascular function and myocardial metabolism in patients with dilated cardiomyopathy

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Dilated Cardiomyopathy (DCM) is a cardiac muscle disease characterized by reduced contractile function and dilation of the left or both ventricular chambers. Classical pathogenetic mechanisms of DCM, such as genetic etiology, viral etiology and autoimmunity, can be considered a leading cause of DCM only in the minority of patients. It has been recently hypothesized that coronary microvascular dysfunction, together with