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Physiopathology of the embryonic heart (with special emphasis on hypoxia and reoxygenation)

Physiopathologie du cœur embryonnaire (conséquences de l'hypoxie et de la réoxygénation)

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Abstract

The adaptative response of the developing heart to adverse intrauterine environment such as reduced O_2 delivery can result in alteration of gene expression with short- and long-term consequences including adult cardiovascular diseases. The tolerance of the developing heart of acute or chronic oxygen deprivation, its capacity to recover during reperfusion and the mechanisms involved in reoxygenation injury are still under debate. Indeed, the pattern of response of the immature myocardium to hypoxia-reoxygenation differs from that of the adult. This review deals with the structural and metabolic characteristics of the embryonic heart and the functional consequences of hypoxia and reoxygenation. The relative contribution of calcium and sodium overload, pH disturbances and oxidant stress to the hypoxia-induced cardiac dysfunction is examined, as well as various cellular signaling pathways (e.g. MAP kinases) involved in cell survival or death. In the context of the recent advances in developmental cardiology and fetal cardiac surgery, a better understanding of the physiopathology of the stressed developing heart is required.

Résumé

Lorsque le fœtus est soumis à une oxygénation intra-utérine insuffisante, des mécanismes d'adaptation modifient l'expression du programme génique fœtal, avec des conséquences à court et à long terme sur le système cardiovasculaire. Le cœur embryonnaire ou fœtal soumis à une hypoxie–réoxygénation ne présente pas le même pattern de réponse que le cœur adulte. La tolérance du cœur immature à un manque d'oxygène aigu ou chronique, sa capacité de récupération, ainsi que les mécanismes cellulaires sous-jacents sont encore mal connus. Cette revue traite notamment, des caractéristiques structurales et métaboliques du cœur embryonnaire et des conséquences fonctionnelles de l'hypoxie et de la réoxygénation. Sont aussi examinées les contributions relatives dans le dysfonctionnement cardiaque d'une surcharge calcique et/ou sodique, de la variation du pH intracellulaire et du stress oxydant. La modulation des voies de signalisation cellulaire (par ex. MAPKinases) qui jouent un rôle dans la survie ou la mort des cardiomyocytes embryonnaires au cours de l'hypoxie est également abordée. Dans le contexte des progrès actuels en cardiologie et en chirurgie cardiaque fœtales, une meilleure compréhension des mécanismes impliqués dans la physiopathologie du cœur immature soumis à un stress semble indispensable.

Keywords: Heart; Embryonic; Physiopathology

Mots clés : Cœur ; Embryonnaire ; Physiopathologie

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1. Introduction

The heart is the first organ to become fully functional during vertebrate embryogenesis. An appropriate cardiac development and an adequate pumping activity with normal hemodynamic parameters are of vital importance for a normal growth of the whole embryo and fetus. Although the rapidly growing embryonic heart operates and develops normally in a relatively hypoxic microenvironment, early cardiogenesis is severely affected by hypoxia and the cardiovascular function can be rapidly impaired by O_2 lack. Maternal hypoxaemia, reduction in uterine or umbilical blood flow or acute placental dysfunction generally result in an inadequate oxygenation of the developing heart. It is generally accepted that oxygen deprivation and readmission can disturb electrical activity and contractility, modify energy metabolism, alter ultrastructure, change cell signaling, modulate gene expression, and induce apoptosis. Some factors involved in myocardial reoxygenation injury are Ca^{2+} and Na^{+} overload, changes in pH and osmolality, production of ROS (reactive oxygen species) and RNS (reactive nitrogen species) and accumulation of glycolytic products. The tolerance of the developing heart to accidental hypoxia or ischemia and its capacity to recover are still under debate. This manuscript reviews the reversible or irreversible functional consequences of acute or chronic hypoxia followed by reoxygenation and mainly focuses on the early embryonic period, e.g. during the first month in human, the first 12 days in mouse and the first 6 days in the chick. The deleterious consequences of teratogenic agents (chemical, physical or infectious) on the function of the developing cardiovascular system are beyond the scope of this paper.

2. Structural and functional characteristics of the embryonic heart

Embryonic cardiomyocytes display scanty myofibrils, a few organized sarcomeres and immature sarcoplasmic reticulum. The T-tubules are absent or less developed like in adult atrial, pacemaking and conducting tissues [1]. Because there is neither sympathetic nor parasympathetic extrinsic innervation at the early stages, the response or the adaptation of the embryonic heart to acute or chronic hypoxic stress is located at the level of the myocardium itself. At early stages, there is no differentiated conduction system. In the straight primary heart tube, the overall myocardial slow conduction velocity is sufficient to ensure the delay, necessary for maintaining unidirectional blood flow with a peristaltoid pattern of contraction. Later, during atrial and ventricular chamber formation and subdivision [2,3], the slow conducting atrio-ventricular canal, which functions in a manner similar to the adult AV node, maintains out of phase the ventricular contraction. The base-to-apex sequence of ventricular activation [4] is also a characteristic of the embryonic chick heart until day 6 (stage 29HH, according to Hamburger and Hamilton [5]).

3. Oxygen transport and hypoxia in the developing myocardium

Unlike fetal and neonatal hearts, early embryonic heart has no myocardial vascularization, the coronary vasculature beginning to develop only after day 32–37 in human [6,7], day 12 in mouse [8] and day 5 in chick [9]. Moreover, the embryonic heart functions and develops normally in a relatively hypoxic microenvironment (pO^2: 0–8 kPa). Oxygen and nutrients diffuse directly from the luminal blood, and diffusion in the avascular myocardium can rapidly become a critical limiting factor under even more hypoxic and/or ischemic conditions. In this connection, the rapid thickening of the ventricular wall due to a high growth rate and the lack of intracellular myoglobine combined with a poorly oxygenated microenvironment, can result in a hypoxic stimulus which could trigger myocardial remodeling and vasculogenesis, very likely through the pathway of the hypoxia-inducible transduction factor 1 alpha (HIF-1α) [10–13]. During normal cardiogenesis the convective oxygen supply progressively supplements the diffusive oxygen transport to meet the metabolic requirements of the immature myocardium [14]. Nevertheless, any short-term or long-term reduction in oxygen supply may rapidly have deleterious functional (e.g. contractility) and structural (e.g. remodeling) consequences.

4. Energy metabolism of the embryonic heart under normoxia and hypoxia

Normal cardiac morphogenesis and function depend on both aerobic and anaerobic energy-producing pathways, i.e. oxidative phosphorylation and glycolysis. During early cardiogenesis, the major energy-consuming functions are cell proliferation and differentiation, morphogenetic movements, apoptosis, homeostasis (maintenance of ion gradients), biosynthesis (proteins, lipids) and mechanical work (contractile activity). Energy consumed by biosynthetic activity is important in the rapidly growing heart since the myocardial protein content can triple within 24 h, e.g. between stage 20 (day 3) and 24HH (day 4) in the chick embryo. This is illustrated for example by the fact that the ratio of the basal O_2 consumption (arrested heart) to total O_2 consumption (beating heart at rest) is 70% whereas it is only 30–50% in neonatal or adult heart [15]. It should also be mentioned that during early embryogenesis cardiac mechanical work increases geometrically, doubling within 24 h and requiring a rapid adjustment of the energy-producing pathways [16]. Although the mitochondrial oxidative capacity of the embryonic chick heart (0.2–0.4 nmol O_2 h^{-1} per μg protein) is rather moderate (i.e. about half of that in the mature myocardium) the activity of the working ventricle depends predominantly on aerobic ATP synthesis as in the adult [15,17]. This is confirmed by the rapid decline of ventricular contractility (i.e. decreased myocardial shortening with contracture, reduction in velocities of contraction and relaxation) during hypoxia or anoxia [18,19] (Fig. 1). Furthermore, oxygen consumption and contractile activity of embryonic chick cardiac myocytes conform to graded hypoxia between $pO^2 < 0.1$ and 16 kPa, while