Regulatory Toxicology and Pharmacology 76 (2016) 221–230

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Animal models of myocardial infarction: Mainstay in clinical translation

Mukesh Kumar [a, *, 1], Eshvendar Reddy Kasala [a], Lakshmi Narendra Bodduluru [a], Vicky Dahiya [a], Dinesh Sharma [a], Vikas Kumar [b], Mangala Lahkar [a, c]

[a] Department of Pharmacology & Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Guwahati 781032, Assam, India
[b] Department of Pharmaceutics, Indian Institute of Technology (BHU), Varanasi 221005, Uttar Pradesh, India
[c] Department of Pharmacology, Gauhati Medical College, Guwahati 781032, Assam, India

ARTICLE INFO

Article history:
Received 8 November 2015
Received in revised form
5 March 2016
Accepted 7 March 2016
Available online 14 March 2016

Keywords:
Ischemia
Reperfusion
Infarction
Animal model

ABSTRACT

Preclinical models with high prognostic power are a prerequisite for translational research. The closer the similarity of a model to myocardial infarction (MI), the higher is the prognostic value for clinical trials. An ideal MI model should present cardinal signs and pathology that resemble the human disease. The increasing understanding of MI stratification and etiology, however, complicates the choice of animal model for preclinical studies. An ultimate animal model, relevant to address all MI related pathophysiology is yet to be developed. However, many of the existing MI models comprising small and large animals are useful in answering specific questions. An appropriate MI model should be selected after considering both the context of the research question and the model properties. This review addresses the strengths, and limitations of current MI models for translational research.

1. Introduction

In the 21st century, cardiovascular diseases (CVDs) are one of the global causes of mortality (Bax et al., 2012; Alwan, 2011), possess the greatest challenges for biomedical researchers (Roger et al., 2011). CVD is a broad term includes hypertension, coronary heart disease, congestive heart failure, and stroke. CVDs account for 17.3 million deaths per annum globally (Reeve et al., 2005). Among all CVDs, Myocardial infarction (MI) accounts for 10% of the total mortality (Alexander and Bruneau, 2010). The second global MI task force definesMI on the basis of specific biomarker troponin I (cTnI) and ECG abnormalities. MI is defined as the detection of the rise and/or fall of cTnI with at least one value above the 99thpercentile with a variation coefficient 10% of an apparently healthy adult population (>0.06 ng/ml) associated with electrocardiographic changes and/or symptoms suggestive of myocardial ischemia (Bax et al., 2012). The clinical course of MI is believed to be influenced by environmental and genetic risk factors. However, an appropriate model should be chosen after considering both the model characteristics and the research context. Most of the laboratory animals have similar human physiology and have an intense translational capability from “bench to bed”, but nowadays ethical approval is being main concern with use of animals.The main purpose of this article is to describe some of the experimental animal models which will bridge the gap between disease and the underlying molecular processes involved.

2. Pathophysiology of MI

Myocardial infarction (“heart attack”) is the irreversible injury of *myocardium* due to prolonged ischemia and hypoxia. MI is clinically characterized by the cardinal symptoms of varying degree of chest pain, sweating, lethargy, difficulty in breathing and sometimes the individual may become unconscious and may even die. Various cardiovascular risk factors such as dyslipidemia, hypertension, diabetes, obesity, food habits, smoking, and physical inactivity, are contributing to the development of CVDs (Upaganlawar et al., 2011). The pathological hallmarks of MI are increased cTnI and/or ECG abnormalities and necrosis of cardiac cells. The

* Corresponding author. Department of Pharmacology, Gauhati Medical College & Hospital, Guwahati 781 032, Assam, India.
E-mail addresses: budhanimukesh1991@gmail.com (M. Kumar), ishreddy4@gmail.com (E.R. Kasala), laxmi.naren21@gmail.com (L.N. Bodduluru), dahiya.vicky681@gmail.com (V. Dahiya), sharma231088@gmail.com (D. Sharma), vikas.phe@iitbhu.ac.in (V. Kumar), dr_mlahkar@rediffmail.com (M. Lahkar).
[1] Present address. Department of Pharmaceutics, Indian Institute of Technology, Banaras Hindu University, Varanasi 221005, UP, India.

http://dx.doi.org/10.1016/j.yrtph.2016.03.005
0273-2300/

pathophysiology of acute myocardial infarction is very complex. Atherosclerosis is the prominent cause of MI. Coronary atherosclerosis becomes complicated by subsequent rupture of atherosclerotic plaque followed by occlusion of coronary artery via formation of a thrombus. This leads to sudden induction of ischemia throughout the anatomic region supplied by occluded artery. Under ischemic condition mammalian cardiomyocytes are unable to produce enough energy in the form of ATP via oxidative phosphorylation which halts the aerobic metabolism. As a consequence myocardial ATP deplets and anoxic metabolism products such as lactic acid accumulates, within seconds (Frangogiannis, 2008). These events result in generation of reactive oxygen species (ROS), reactive nitrogen species (RNS), calcium imbalance, and disturbance in cell metabolism. ROS and RNS induce oxidative stress, which transmogrifies membrane permeability and cellular proteins (Ceconi et al., 1991). Ischemia reduces cardiac output and arterial pressure resulting in stimulation of baroreceptor followed by activation of neurohumoral compensatory mechanisms. The pain and anxiety associated with myocardial infarction also aggravates the condition by further activating the sympathetic nervous system (SNS). Over activation of sympathetic nervous system leads to systemic vasoconstriction and cardiac stimulation causing increase in myocardial oxygen demand that leads to greater myocardial hypoxia, increase in the infracted region, precipitate arrhythmias, and further impair cardiac function. The outcome of these insult are ultra-structural changes of cardiomyocytes, disruption of the sarcolemma, DNA damage, coagulation necrosis and ultimately cell death. Cardio preventive strategies are not yet available but are one of the priorities in current MI research (See Fig. 1).

3. Animal models for translational research in MI

The use of animal models of cardiovascular disease is an obligatory step for the understanding of mechanisms and any kind of therapeutic approach. Animal models are the preliminary tools in drug development; which provides better understanding of disease pathophysiology. They also provide new approaches to amend the diagnosis and treatment of diseases (Zaragoza et al., 2011). Progress in understanding the etiology of MI has provided candidate targets for cardio-protective interventions. To understand the underlying pathophysiology, and progression of ischemia to myocardial infarction animal models gain very much interest to subdue the hindrance of clinical studies. Preclinical MI studies help in hypothesizing new strategies in the diagnosis, prevention and treatment and translation in to clinical settings (Liu and Li, 2012). However, to date, no potential protective treatment has received regulatory approval. One reason for this is the lack of good MI animal models for preclinical translational research. Animal models should fulfill specific requirements for the testing of cardio-protective therapies for MI.

In small animals induction and development of coronary atherosclerosis is very challenging. However in the evolving era of science and technology, various transgenic and newer animal models are available which helps in the development of emerging technologies in interventional pharmacology. List of available preclinical MI models are illustrated in Fig. 2.

Small animals including mice, rats and rabbits are frequently used lab animals for cardiovascular research because of their small size, relatively inexpensive, ease in handling and maintenance (Recchia and Lionetti, 2007). However there are some disadvantages in the use of small animal models such as small heart size and anatomical differences in coronary artery (Ciszek et al., 2007) and conduction system anatomy from human (Meijler, 1985) makes it high failure rate in the clinical translation “from bench to bed”. Large animals such as pig, porcine, dog and sheep are more resemble to humans, in context to minimal preexisting coronary collaterals and similar coronary anatomy and physiology. For example dog heart resembles to human with few differences like high collateral circulation and left prevalence of coronary vasculature (Blumgart et al., 1950). While the porcine and swine have similar minimal collateral circulation and dominant right coronary vasculature to that of humans (Weaver et al., 1986; Maxwell et al., 1987). The metabolic activity of swine heart is similar to humans as they utilize non-esterified fatty acids for energy production (Maxwell et al., 1987). Currently pigs are widely used in

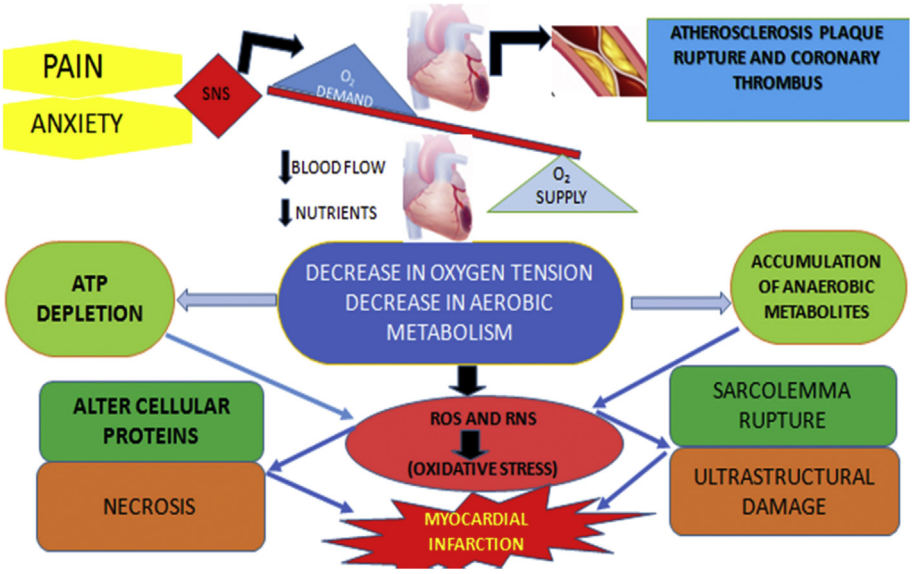

Fig. 1. Pictorial representation of MI: Atherosclerotic plaque and coronary thrombus formation leads to decrease in blood flow or ischemia. As a consequence there is an imbalance between coronary blood demand and supply. Pain and anxiety activates sympathetic nervous system (SNS) which further increase oxygen demand via constricting peripheral arteries. Ischemic condition halts the oxidative phosphorylation results in accumulation of anaerobic metabolites, depletion of ATP concentration and generation of ROS and RNS or oxidative stress. ROS/RNS having potential to alter the cellular proteins, causes sarcolemma rupture, ultra structural changes, necrosis of cardiac myocytes followed by irreversible injury/myocardial infarction.