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Ischemia/reperfusion injury in male guinea pigs: An efficient model to investigate myocardial damage in cardiovascular complications

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ABSTRACT

Myocardial ischemia/reperfusion (I/R) injury is the major problem that aggravates cardiac damage. Several established animal models fail to explain the similarity in disease mechanism and progression as seen in humans; whereas guinea pig shows high similarity in cardiovascular parameters. Hence, current study is aimed to develop an animal model using guinea pigs that may best correlate with disease mechanism of human myocardial I/R injury. Male guinea pigs were randomized into three groups: normal diet (ND), high fat diet (HFD) and sham; fed with respective diets for 90 days. Myocardial infarction (MI) was induced by ligating left anterior descending artery (LAD) for 30 min followed by 24 h and 7 days of reperfusion in ND and HFD groups. Electrocardiogram (ECG) showed the alterations in electrical conduction during myocardial I/R injury. Elevated levels of lactate dehydrogenase (LDH) and creatine kinase-MB ((CK-MB)) were higher in HFD compared to ND. Inflammatory markers such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were up-regulated in I/R injury animals compared to sham. Fold change of these protein expression levels were higher in HFD compared to ND. Elevated lipid profile and increased aortic wall thickness in HFD animals depicts the risk of developing cardiovascular complications. ECG analysis strongly confirmed MI through changes in sinus rhythm that are reflected in infarcted tissue as verified through TTC staining. Thus the combination of HFD followed by I/R injury proved to be an efficient model to study pathophysiology of myocardial I/R injury with minimal tissue damage and surgical mortality.

1. Introduction

Cardiovascular diseases (CVDs) are the foremost cause of mortality and socioeconomic burden worldwide [1]. According to the World Health Organization (WHO) and the American Heart Association (AHA) 31% of global deaths and 1 death in every 40 s in the US is due to CVDs. The prevalence is higher in low and middle income countries. In India, 4 deaths per minute and 2.5 million deaths every year is due to CVDs [2,3]. Occlusion of coronary artery due to atherosclerotic plaque is the catastrophic cause of myocardial infarction (MI) and leading cause of death worldwide [4]. Dietary fat has a significant effect on the incidence of cardiovascular diseases due to the formation of atherosclerotic plaque [5]. Reperfusion of coronary arteries by use of thrombolytic therapy and surgical intervention are the available treatments to resuscitate damaged myocardium [6]. Reperfusion is a double edged sword, reperfusion induced injury contributes to severity of the infarction [7,8,9]. Despite improvements in cardiovascular care, management and treatment, the rate of mortality and re-hospitalization are significantly increasing over years [10,11] and burden of CVDs is higher. Even after the decades of research the complex mechanism and drug targets are not completely explored to culminate the deleterious effect of myocardial I/R injury. Currently mouse and rat models are the most common animal models for this purpose. However there are some pitfalls and therefore it is noteworthy to make an attempt in developing a more suitable animal model that may help to develop sensitive diagnostic methods for early detection, identification of novel therapeutic targets, affordable therapies and long term disease management. MI models to mimic atherosclerosis in rats, mice, rabbits and pigs that were

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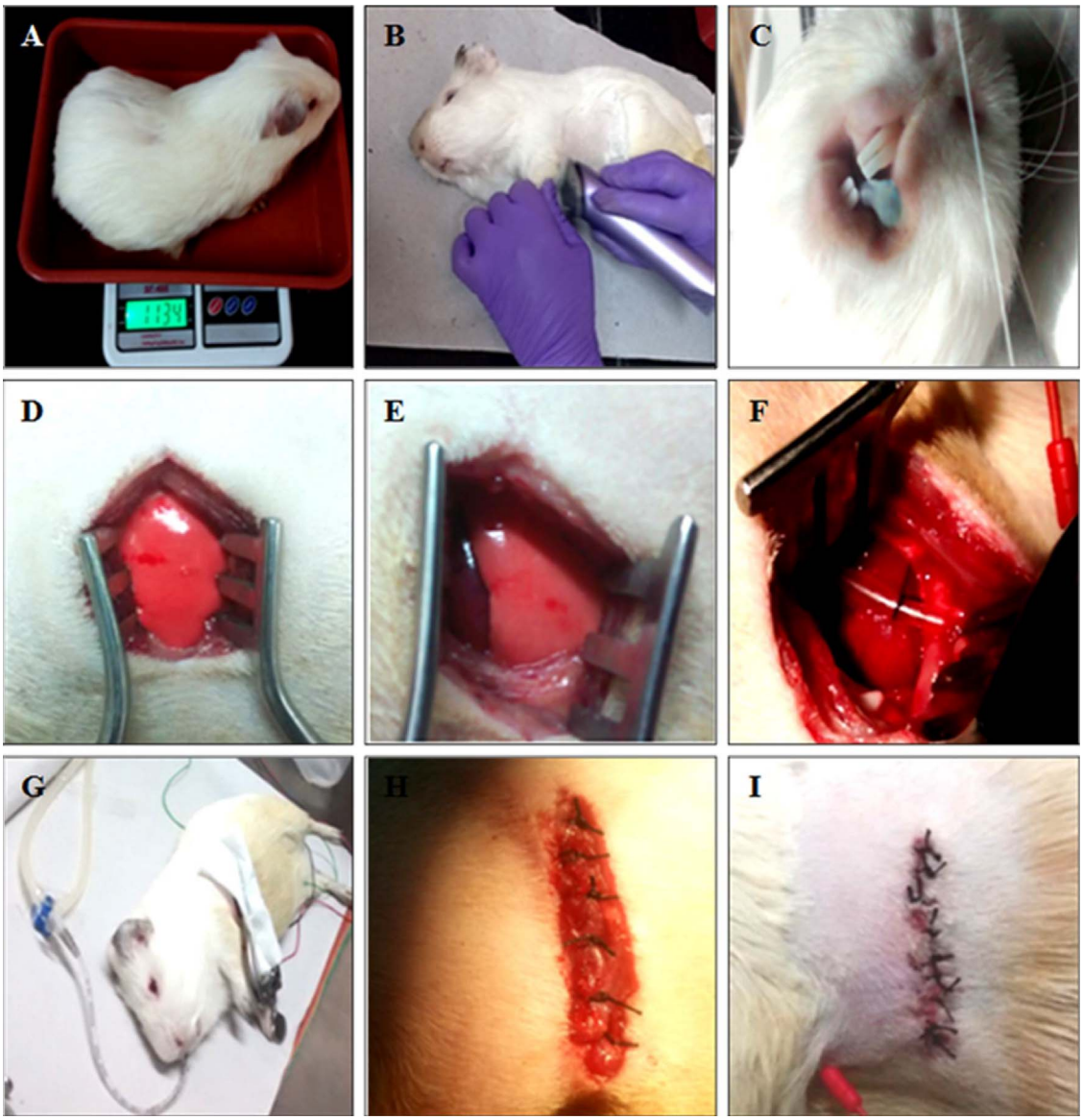

Fig. 1. Photographs of various steps involved in the induction of myocardial ischemia/ reperfusion injury (A) Body weight of guinea pig (B) Preparation of surgical site (C) Endotracheal intubation (vapor deposition on glass slide) (D) Exposure of lung after thoracotomy (E) Position of lung and heart (F) LAD ligation (G) Thirty minutes of ischemia after ligation (H) Ribs and muscle layer was sutured (I) Closed surgical site.

fed with high fat/cholesterol diet, followed by Left Anterior Descending artery (LAD) ligation [12,13] are well established. But it is well known that rats and mice are not suitable models to study atherosclerosis as they are tolerant to high fat diet and their fatty acid metabolism and lipid profile differ from humans [14]. Other models include knock out or knock down mice; however, progression and prognosis of disease varies and gene manipulations may not provide complete relevance [15].

Guinea pigs are considered as the best animal model to study atherosclerosis induced MI, as they have many similarities to humans such as ventricular action potential, lipoprotein profile, cholesterol metabolism and higher levels of free cholesterol compared to esterified cholesterol [14,16,17]. Compare to other rodents, guinea pig hepatocytes has the capacity to edit mRNA of ApoB100, facilitating lipoprotein metabolism more similar to that of humans making them sensitive for dietary fat saturation, dietary cholesterol and dietary fiber by altering LDL-C [18]. Guinea pigs possess vital proteins that are responsible for lipoprotein remodeling and reverse cholesterol transport such as CETP, lecithin:cholesterol acyltransferase (LCAT), and lipoprotein lipase (LPL) implicating that guinea pigs has equivalent lipoprotein metabolic events as that of humans [19]. Modified lipoprotein like oxidized LDL is considered as an important parameter for the development of inflammatory response in the humans and is well studied in the guinea pigs [20].

Surgical induction of MI by LAD ligation is well described in rats and mice [21,22]. It is challenging in guinea pigs due to difficulties related to ligation that include the need for artificial ventilation requiring endotracheal intubation through tracheotomy. This “second surgery” is linked to higher risk of tissue damage and infection [23]. Direct endotracheal intubation in guinea pigs without tracheotomy is complicated due to the anatomy of the oral cavity and the large tongue that masks the larynx [24]. Overcoming this challenge using advanced technologies will make guinea pigs as an impeccable model and pave way in understanding key pathophysiological events. The present study therefore aimed to design a simple, accurate and novel myocardial I/R injury model in guinea pigs and to analyze the effect of high fat diet

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