

**REVIEW ARTICLE**

# To develop a novel animal model of myocardial infarction: A research imperative

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**Abstract**

Although great progress has been made in therapeutic interventions for coronary artery disease (CAD), it is still the deadliest disease in the world. Currently animals that are similar to human beings in their cardiovascular pathophysiology are being used to explore the pathogenesis and therapy of CAD. There have been a series of developments in creating CAD animal models using mice, rats, rabbits, dogs, and pigs, but unfortunately there is still no acceptable model for human CAD. The ideal CAD animal model should satisfy several conditions as follows. First of all, it should have a pathophysiological process for CAD that is similar to humans. Second, it should be useable for assessing drug efficacy. The last and most important condition is that the model can be used to duplicate clinical therapeutic skills. The limitations of current methods for making animal models have meant that these models not only do not duplicate the actual pathogenesis, but also cannot be used to simulate clinical therapy, and do not support scientific evaluation of drug efficacy. Therefore, the development of a fit-for-purpose animal model for CAD is imperative for future research. Such a development will lead to rapid progress and greater efficiency in CAD research. This paper summarizes the present situation in the field of CAD animal models, and puts forwards ideas for developing a novel animal model of myocardial infarction.

**KEYWORDS**

animal model, atherosclerosis, coronary artery disease, myocardial infarction

**1 | INTRODUCTION**

Although we have made great advances in the treatment of coronary artery disease (CAD), it remains an important public health challenge. It is currently the disease with the highest mortality in the world. With changes of lifestyle, more and more Chinese suffer from CAD, which constitutes a serious threat to the Chinese people and their society. Accordingly, more and more scientists are focusing their researches on this area.

Although great progress has been made in the treatment of CAD using drugs, thrombolysis, surgical interventions and gene therapy, there are still many challenges in CAD research that need to be resolved because the pathogenesis of this disease is not yet fully understood. At present, CAD is regarded as a disease involving multiple genes, with genetic and environmental factors interacting. Many experiments cannot be directly carried out in the human body for various reasons. Fortunately, in some animals the pathology of CAD is similar to that in humans, and therefore establishing an animal

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model for CAD would be an effective method for further exploring its pathogenesis and pathological processes and developing novel therapies.

## 2 | CURRENT RESEARCH ON ANIMAL MODELS OF CAD

CAD animal models have been tried with a variety of animals and methods, each with their advantages and disadvantages, but most animal models are different from humans in pathological process and corresponding symptoms. CAD is a myocardial dysfunction and/or organic lesion caused by coronary stenosis and insufficient blood supply. It is also known as ischemic cardiomyopathy. Hypertension, diabetes, obesity, cigarette smoking and “bad habits,” leading to the formation of atherosclerosis (AS), are the main causes of the disease. Myocardial ischemia is a characteristic of physiological and pathological changes caused by AS. The pathological changes in CAD include lipid infiltration, fatty streaks, atherosclerotic plaques and fibrous atherosclerotic plaque compound lesions. It is termed CAD when the coronary artery stenosis area caused by AS occupies 51% to 75% or more of the original area.<sup>1</sup> Myocardial ischemia (MI) occurs when the blood flow through the coronary artery is completely interrupted by plaque rupture, bleeding, or spasm, and ischemic necrosis occurs in the myocardium deprived of its blood supply. Therefore, in order to provide an ideal research medium for further exploring the pathogenesis, pathological process and effective treatment of CAD, and to make an objective evaluation of drugs or therapeutic methods, animal models with a pathological process similar to human CAD should be established to match the clinical situation as closely as possible.

Because of its small size, low cost, and fast reproduction, mouse has become the most commonly used animal model in the field of cardiovascular research. Both the apolipoprotein E knockout (ApoE KO) mice and the low density lipoprotein receptor knockout (LDL-R KO) mice are very popular due to their susceptibility to AS. They present with coronary AS, myocardial ischemia/infarction, and heart failure. Although ApoE KO mice and LDL-R KO mice can form obvious AS under a high-fat diet, the plaques are mainly distributed in the aorta and its outflow tract, and less in the coronary artery. Therefore, the current CAD model in mice mainly depends on coronary artery ligation or isoproterenol injection.<sup>2</sup> This type of model and method cannot simulate the natural pathogenesis of human CAD and has obvious limitations since the underlying causes of CAD are not present.

Rats have the convenient characteristics of easy feeding, good survival rates and low maintenance cost, but there is no gallbladder in rats, so the absorption rate of exogenous cholesterol is low. In addition, because of the rat's characteristic of spontaneous anti-AS formation, it is difficult to induce AS lesions by high-fat diet alone. Moreover, it has been found that there is an inter-adjustment state of plasma lipids and significant anorexia in the process of hyperlipidemia establishment in rats by high-fat diet feeding.<sup>3</sup> Therefore, most research has used a drug and/or injury combined method to form AS lesions.<sup>4</sup> Although the morphology of the AS lesion and the

rupture position of the plaque in rats are similar to those in humans,<sup>5</sup> this mode of modeling is still different from the natural pathogenesis of human CAD.

Rabbits are the most commonly used animal model of hyperlipidemia and AS.<sup>6</sup> They are sensitive to high-fat diet, and their absorption rate of exogenous cholesterol is up to 95%. They easily convert exogenous cholesterol into blood lipids, and have a low clearance rate of these lipids. However, rabbits are herbivores, with large differences in lipid metabolism from humans. The atherosclerotic plaques are formed mainly in the thoracic aorta, and coronary lesions mainly in small arteries in rabbits, while those in humans are formed mainly in large branches of the coronary arteries. The anatomy of the heart, coronary branches, coronary artery travel and coronary collateral circulation in rabbits are similar to those of humans. Arrhythmia due to coronary artery occlusion has a lower mortality rate in rabbits.<sup>7</sup>

The cardiovascular system in canine models is well developed, and the nervous and humoral regulation systems are perfectly matched to the human system, while the volume is sufficient to get enough information. However, dogs have an extensive sidelimb circulation, large coronary artery variation, and some have wall arteries. The distribution of the left anterior descending branch is often broader than the left circumflex. Both of the branches can be easily ligated to make a myocardial ischemia model. Dogs are not good animal models of AS, however, because they cannot develop AS spontaneously, even under high-fat diet conditions, as is the case for rats and mice.<sup>8</sup>

The physiology, anatomy, blood lipids, AS lesions, and lipoprotein metabolism mechanism in pigs are close to those in humans,<sup>6</sup> suggesting they would make a better model for mimicking human AS. The distribution, histological structure and pathogenesis of atherosclerotic plaques are similar to those of humans. The model of MI formed after the occlusion of the coronary artery branches is comparable to that of human MI.<sup>9,10</sup> However, the pig's body shape, body signs and living habits are quite different from those of humans, and the model's production cycle is also very long. There are still many physiological discrepancies between pigs and primates.

The sheep myocardium shares many similarities with humans. For example, the predominant myosin heavy chain isoform in sheep is the slow  $\beta$ -MHC, as in humans.<sup>11</sup> Various disease types can be developed in sheep, including, but not limited to, MI and gradual aortic constriction-induced heart failure. Most notably, sheep models are more expensive to produce and maintain in animal facilities than other small animal models. Compared with the intraperitoneal injection and intravenous injection of small animal models, another technical limitation is that adeno associated viruses are required to transduce sheep myocardial tissue.

## 3 | PRIMATES ARE POTENTIALLY IDEAL ANIMAL MODELS OF CAD

For practical purposes, the study of medicine must be based on scientific experiments in animals and the animal species must be

similar to humans in physiology and pathology. Theoretically, nonhuman primates are the most suitable for medical research because of their similarity to humans in genetic evolution, immunity, physiology, metabolism, and so on. Nonhuman primates are the best experimental models for the study of chronic diseases in humans because they have a long life cycle and similar biological characteristics to humans. Animal models of human diseases established in non-human primates allow observation of the occurrence and development of the disease, as well as the complications. They also provide a reliable medium for efficacy testing of drugs and safety evaluation.

*M. fascicularis*, also known as *Cercopithecus* or the Javanese monkey, belongs to the primate monkey family and lives in mangrove swamps. Compared with other nonhuman primates, *M. fascicularis* monkeys have more advantages as a potential animal model. First of all, they live all over the southeast Asian regions, such as Indonesia, Vietnam and The Philippines, providing a rich low-cost resource. Second, their small size, long tail and gentle character make them easy to catch. Third, they have a short breeding cycle with no seasonality and their smaller size requires lower drug dosages. In addition, in recent years, a large amount of genomic information about this species has been added to the NCBI, EBI and other databases,<sup>12,13</sup> which has led to wider use of *M. fascicularis* in medical research. At present, there are no CAD animal models using *M. fascicularis* monkeys, but it is foreseeable that once such a model has been established successfully, it will be widely used in life science research.

#### 4 | THE NEED TO DEVELOP A NOVEL ANIMAL MODEL OF MI

At present, MI models can be divided into two types. One is an acute model and the other is a chronic model. The acute model is usually made by coronary artery ligation, interventional embolization, or drug induction. Essentially, coronary artery ligation and interventional embolization are very similar. Both of them occlude the blood stream using external objects, which leads to the pathological process of MI. Recently, thrombosis models have been widely used. Kwiatkowski et al<sup>14</sup> used an interventional method to inject autologous thrombus into coronary artery, which causes MI and the related pathological process. However, this operation has a high mortality rate. Drug induction is very simple. It usually uses abdominal, caudal or sublingual vein injection of pituitrin or isoproterenol, which can result in short-term MI. However, all of these methods lack the pathological process of AS development, which is the basis of a real acute MI.

The chronic CAD model can generally simulate the natural pathogenesis of CAD. It can be used to study the pathological processes of CAD. The methods of making these models include interventional oppression, high-fat diet, and high-fat diet combined with drugs or ligation. In essence, interventional oppression gradually reduces the inner diameter of vessels by using exogenous objects, such as ameroid rings, balloons, water sacs, or air sacs. It can result in myocardial ischemia as well as the corresponding lesion process. In practical terms, interventional oppression is similar to use of ligation and

interventional catheters in making acute models, except that it takes longer to establish the model. It is not completely consistent with clinical myocardial ischemia caused by AS.

The high-fat diet method involves feeding the experimental animals with rich cholesterol foods for a relatively long time. It induces hyperlipidemia, AS and sclerotic plaques, which result in stenosis in the blood vessel and myocardial ischemia. This method is closest to the clinical pathological and physiological processes of CAD. It is better for observing the pathology of CAD and for comprehensive efficacy testing of drugs, but it requires longer to prepare the model and the degree of ischemia is also difficult to control. At present, this method is successfully used with rats and rabbits.<sup>15,16</sup>

A combination of drugs and ligation following a high-fat diet can be used. The animal is first fed with a high-fat or high-cholesterol diet for a long period, which induces lipid metabolism disorder and gradual appearance of AS. Myocardial ischemia can then be induced by a combination of drug injection and ligation. Using this technique, the pathological changes and mechanisms, and the treatment effect of the drugs on blood lipids, vascular lesions and heart injury can be conveniently studied. The drug-induced effects are usually unstable and ligation requires high surgical skill. Moreover, this model cannot be used to explore autolysis recanalization in the clinic, and hence this method is not ideal.

Clinically, CAD predominantly occurs in middle-aged or aged people. It is a disease involving multiple genes, and genetic and environmental factors play important roles in its development. It has a close relationship with hypertension, high fat and glucose intake, obesity, smoking and lack of exercise. It forms gradually on the basis of AS. From this point of view, the animal models generated using a high-fat diet are the closest to a real CAD patient. However, this is a time-consuming method and it is difficult to accurately regulate myocardial ischemia. Therefore, these defects cannot be ignored.

Recent developments in interventional technology provide a potentially ideal model for the study of the pathogenesis of coronary artery thrombosis. It avoids trauma caused by thoracotomy and reduces model mortality. However, because current interventional embolization often uses micro-embolism balls, metal emboli and chemical embolism agents,<sup>17</sup> the blood vessel cannot be recanalized after vascular embolization. In addition, the pathogenesis is still different from human CAD, and it is not scientifically possible to use the technique to verify the efficacy of the drugs, especially to observe whether the coronary thrombosis can be recanalized under drugs; therefore, further development of innovative animal models of CAD is needed.

#### 5 | DISCUSSION

The disadvantages of current CAD models, summarized above, confirm that an ideal animal model needs to be established. The key problems to be solved are simulation of autologous coronary artery plaque formation and triggering of plaque rupture by the researchers.

An ideal model should have these requirements: (1) it follows the natural pathophysiological process of CAD, (2) it can be used to observe the curative effect, mechanism and functional features of anti-myocardial ischemia drugs, thrombolysis and interventional therapy, (3) it can be used for long-term, continuous, systematic observation, (4) it should allow controlled, repeatable uncomplicated experiments, without side-effects, and the animals should be easy to operate, with a low mortality rate, (5) all animal experiments should be able to be approved by Animal Ethics Committees.

In summary, using modern science and technology such as molecular biology, the development of a fit-for-purpose CAD animal model is an important and imperative task for further exploration of the pathogenesis and pathological process of CAD, and of effective treatment methods and new drugs. Once a significant breakthrough is made, it will certainly be a powerful impetus to the development of CAD research.

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#### CONFLICT OF INTEREST

None.

#### AUTHOR CONTRIBUTIONS

All listed authors meet the requirements for authorship. YPT undertook the conclusion of all information and the writing of this article. YL provided support with information retrieval and text editing. YJF, YYZ, JQF and YL provided the original drafts. YPT acts as guarantor. All authors read and approved the final manuscript.

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