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Experimental Animal Models in Heart Disease

Kalp Hastalıklarında Deney Hayvanı Modelleri

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ABSTRACT

Heart diseases constitute a significant global burden of mortality and morbidity. This encompassing word refers to a variety of illnesses, including coronary artery disease, heart failure, myocardial infarction, and valvular heart disease. Given the imperative need to comprehend and address these ailments, experimental studies are indispensable. Experimental animal models serve as indispensable tools in elucidating the mechanisms of heart disease. They are pivotal for developing novel treatments and assessing the efficacy of existing therapies. Among the commonly utilized animal models in heart disease research are mice, rats, rabbits, dogs, and pigs. Each model offers distinct advantages and limitations, allowing researchers to probe specific facets of cardiac pathology and unravel the intricate mechanisms involved in heart disease. In this comprehensive review, it was aimed to provide a succinct overview of the various animal models employed in heart disease research. The advantages and drawbacks of each model were delineated, the aspects of human heart disease they emulate were elucidated, and pivotal research findings facilitated by their utilization were highlighted. By synthesizing this information, it was the endeavor to provide researchers and clinicians with valuable insights into the diverse array of animal models available for investigating heart diseases, ultimately paving the way for enhanced understanding and treatment of these debilitating conditions.
Keywords: Coronary artery disease; heart failure; myocardial infarction; rodents; ischemia.

ÖZ

Kalp hastalıkları, dünya çapında önemli bir ölüm ve hastalık yükünü oluşturur. Bu genel terim, koroner arter hastalığı, kalp yetmezliği, miyokard enfarktüsü ve kapakçık kalp hastalığı gibi çeşitli durumları kapsar. Bu hastalıkları anlama ve ele alma gerekliliği göz önüne alındığında, deneysel çalışmalar kaçınılmazdır. Deneysel hayvan modelleri, kalp hastalıklarının mekanizmalarını açıklamada vazgeçilmez araçlar olarak hizmet eder. Yeni tedaviler geliştirmek ve mevcut tedavilerin etkinliğini değerlendirmek için kilit öneme sahiptirler. Kalp hastalığı araştırmalarında yaygın olarak kullanılan hayvan modelleri arasında fareler, sıçanlar, tavşanlar, köpekler ve domuzlar bulunmaktadır. Her model, araştırmacıların kalp patolojisinin belirli yönlerini incelemesine ve kalp hastalığında rol alan karmaşık mekanizmaları çözmesine olanak tanıyan farklı avantajlar ve kısıtlamalar sunar. Bu kapsamlı incelemede, kalp hastalığı araştırmalarında kullanılan çeşitli hayvan modellerinin kısa bir özetinin sunulması amaçlanmıştır. Her bir modelin avantajları ve dezavantajları belirlenmiş, insan kalp hastalığını taklit ettikleri yönleri açıklanmış ve kullanımlarına olanak tanıyan önemli araştırma bulguları vurgulanmıştır. Bu bilgileri sentezleyerek, araştırmacıların ve klinisyenlerin kalp hastalıklarını araştırmak için mevcut çeşitli hayvan modellerine sağladığı değerli bilgilerle, bu rahatsız edici durumların anlaşılmasının ve tedavisinin geliştirilmesine katkıda bulunmak amaçlanmıştır.
Anahtar kelimeler: Koroner arter hastalığı; kalp yetmezliği; miyokard enfarktüsü; kemirgenler; iskemi.

INTRODUCTION

There are numerous cardiovascular disorders; some affect the heart (myocarditis, coronary heart disease, hypertension), while others damage the arteries (atherosclerosis) or veins (thrombophlebitis). Myocardial infarction (MI), one of the most prevalent cardiovascular disorders, is an acute condition that causes necrosis of the heart muscle tissue (myocardium) as a result of a complete or partial blockage of blood supply to the heart (1). This condition affects the integrity of the cardiovascular system and can lead to serious complications or death of the patient. Such violations usually occur on the basis of atherosclerosis of the coronary arteries. Atherosclerosis leads to the narrowing of the coronary arteries and damage to the walls of blood vessels, which creates the basis for the formation of blood clots and arterial stenosis. Cardiovascular diseases account for 30% of deaths in Europe and America and 32% worldwide. According to the data of the Turkish Statistical Institute, approximately 505 thousand people died in 2022. Cardiovascular diseases accounted for 34.5% of these deaths. When deaths from circulatory system diseases were analyzed according to sub-clauses of death, it was reported that 42.3% of the deaths were due to ischaemic heart diseases, 23.5% were due to other heart diseases and 19.2% were due to cerebrovascular diseases (2). Among cardiovascular diseases, MI is still one of the leading causes of death and hospitalization in Turkey and worldwide. Today, the incidence of MI is increasing even in people under 40 years of age. MI is usually associated with diseases such as atherosclerosis, hypertension, and diabetes. In most cases, patients usually have a painful form of MI, which allows doctors to accurately diagnose the disease and start treatment quickly (1).

Animals utilized in research serve as crucial assets for comprehending the pathophysiology of diseases and for advancing therapeutic strategies. They are employed in fundamental medical and veterinary investigations. A diverse array of animals has been identified as effective models for studying diseases affecting both humans and animals alike. These research subjects encompass mice, rats, rabbits, guinea pigs, sheep, goats, cattle, pigs, primates, dogs, cats, birds, fish, and frogs (3). Our understanding of the cardiovascular system has substantially increased in recent decades; nonetheless, further study is needed to broaden our knowledge and give new therapeutic possibilities. There is also a need for a good animal model where cardiovascular function and illness may be researched efficiently and reliably, with possible translational applicability to humans (4). Animal models have contributed much to our understanding of the cardiovascular system. Small animals (Drosophila, Zebrafish, Xenopus, mice, and rats), medium-sized animals (Guinea pigs, rabbits, cats), and large animals (dogs, pigs, sheep, and non-human primates) continue to be important in preclinical research. However, criticism of animal-based platforms is emerging because, by definition, animal models represent inaccurate facsimiles of human diseases and disorders with differing genetic backgrounds and disease development mechanisms (5). Cardiac illnesses are frequently created in healthy animal models by genetic, pharmacological, or surgical modification. Certain animal species are better suited for specific induction procedures. Mice are good for creating genetic models, although surgical treatment is typically used on larger rodents and animals such as rats, rabbits, and dogs (4). The rat has been used as a basic model in cardiovascular research for many years (6). Experimental procedures have been developed to induce cardiovascular disease states in this species, such as cardiac hypertrophy and failure, MI, and systemic and pulmonary hypertension. Additionally, rat species that have these diseases spontaneously (congenitally) have also been bred. In order for an animal model developed for any cardiovascular disease in humans to be ideal, it is expected to have 5 important characteristics: a) it should resemble the disease observed in humans and enable chronic disease studies, b) it should produce predictable and controllable symptoms, c) it should be economic-technical, d) it should be acceptable in terms of animal ethics, and e) allow the measurement of heart-related biochemical or hemodynamic parameters.

There are also some difficulties with the models used in cardiovascular system diseases. For example, conditions such as hypertension or heart failure (HF) are slowly developing diseases accompanied by large-scale neuro-humoral adaptations in humans, whereas in animal models these diseases are induced acutely either with the help of surgical methods or drug administration. On the other hand, while cardiovascular diseases are not common in young people, they occur with aging, but the incidence is increasing. In contrast, young adult rats are used in many hypertension and HF studies. The animal model of aging is just beginning to be detailed. Moreover, despite the presence of high blood lipid levels, the development of atherosclerosis is not observed in most species of rats. However, animal experiments also have a very important place in advances in other areas of medicine. For example, almost all advances in cardiac surgery are based on animal experiments (7).

This review aimed to bring together the experimental animal models in heart disease that have been developed to date and to systematically present more understandable and comprehensive data.

ANIMAL TYPES USED IN EXPERIMENTAL MODELS OF HEART DISEASE

Small Rodent Models

Mus musculus (mice) and *Rattus norvegicus* (rats) are essential for animal models of heart illness, with each species providing distinct advantages. Mice and humans share genetic and physiological similarities, therefore genetically modified mouse models are thought to be useful in studying specific cardiac genes and signaling networks. Rats, with their bigger stature than mice, make surgical operations easier, allowing researchers to faithfully recreate human cardiac diseases such as ischemic heart disease and hypertension using techniques such as coronary artery ligation. Their anatomical similarities enable the study of surgical methods and interventional therapies applicable to human patients (8). These studies have helped develop new treatments and test the effectiveness of existing treatments. With thirty thousand protein-coding genes each, mice and rats are the most widely used animal models. Their genomes are highly similar to the human genome (9). Rodent models are frequently used in cardiovascular research because they are easier to handle and house, have a shorter gestation

period, can be genetically manipulated to produce transgenic strains, and have lower maintenance costs; thus, they are better suited for "high throughput" studies than large animal models (10). Because of these qualities, tiny rodent models are the most widely employed in investigations of heart physiology and illness, genetics, pharmacology, and long-term survival (4). However, because rodents are phylogenetically distant from humans, some pathophysiological aspects of disease and their responsiveness to pharmaceutical therapies may not be valid indicators (4,10). Rodent models serve an important role in laboratory-based cardiac research. They have a four-chamber heart structure similar to humans, with high genomic sequence similarity, and are relatively easy to handle, take up less space, and cost less than more evolved species. Mouse models have become the most common due to the widespread availability of genetically modified lines and established techniques for manipulating gene expression. Rats are also extensively employed in laboratories and have superior surgical manipulation and imaging capabilities than mice. Rat models that have been genetically engineered are increasingly being employed (11). The three main approaches to inducing heart disease in rodents are surgical, pharmacological, and gene manipulation (12). Technological advancements have enabled the measurement of many in vivo cardiac parameters in small rodents, complementing molecular, in vitro, and ex vivo functional research. These techniques include echocardiography, cardiovascular magnetic resonance imaging, electrocardiography, pressure-volume loops, and blood pressure measurement (4).

Medium Animal Model

The rabbit is a medium-sized animal with many cellular and molecular traits similar to humans, and it is a viable option for larger mammals. Several rabbit models are employed, including pressure or volume overload, ischemia, fast pacing, doxorubicin, drug-induced arrhythmias, transgenesis, and infection. These models also aid in the evaluation of therapy methods that may prove effective in human heart illness (13). Because of its medium size, rabbits have various potential benefits over other animals. Although the rabbit heart is smaller than that of a dog or a pig, it is large enough to allow for surgical and catheter-based therapies at a significantly reduced cost (5-15 times less expensive than those of dogs). At the same time, several 'adult human scale' therapies have been or are being scaled down for pediatric usage and assessment (e.g., pacemakers and CRT), allowing rabbit models to be useful. In rodents, surgical interventions remain more straightforward than microsurgical methods. More critically, rabbit cardiac physiology resembles human cardiac physiology more than mice or rats (14). Indeed, cellular electrophysiology and Ca++ transport in rabbits are more similar to those in humans than in rats or mice (15). This is especially important for research into HF and arrhythmias since changes in ion channel and Ca++ transporter function or expression are hypothesized to contribute directly to poor contractile performance and arrhythmogenesis (16).

Large Animal Models

The primary benefits of in vivo studies using large mammalian hearts are that: a) they can legitimately claim to be physiologically and/or clinically optimal, b) they allow for chronic studies, c) they allow for assessment of cardiac function and responses in the intact animal, and d) they are probably the best model for new drug screening and toxicity testing due to their conserved molecular mechanisms with humans rather than small animals such as rodents (17,18). However, it is important to recognize that these animal models are not representative of human ischemic heart disease. Most animal experiments use the abrupt closure of a coronary artery in previously healthy tissue. This is very different from the complex and progressive development of human cardiovascular disease, which includes underlying vascular disturbances as well as genetic and environmental components. There are also cost and logistical issues with employing large animal models. Most notably, large animal models are significantly more expensive to purchase and maintain in animal facilities than small animal models; daily housing fees for large animals are 30 to 90 times higher than those for mice (4,18).

Because of their close resemblance to human physiology, canine models are especially useful for studying conduction physiology and rhythm problems, as well as research based on heart rate, oxygen intake, and contractility. They have proven to be suitable candidates for long QT syndrome (LQTS) study as well as studies of Duchenne muscular hypertrophy, Brugada syndrome, and cardiac failure. Porcine models (*Sus scrofa domesticus*) are differentiated by their anatomical similarity to the human coronary circulation, making them ideal models for the study of myocardial ischemia and infarction. Their applications include the study of post-infarction remodeling, regenerative treatment methods, and interventional cardiology procedures. Ovine models (*Ovis aries*) play an important role in the advancement of cardiac surgery, cardiovascular interventions, medical device testing, hemodynamic studies, pharmacological research, and cardiovascular imaging due to their anatomical and physiological similarities to humans, as well as their manageable size. Less common models, such as non-human primates like macaques and baboons, are widely employed in atherosclerosis research to investigate the effects of dietary changes, innovative pharmacological regimens, and cardiac imaging studies (8).

THE MOST COMMON ANIMAL MODELS USED TO STUDY HEART DISEASE

Models of Myocardial Infarction

MI is the most severe clinical manifestation of coronary heart disease in particular and is the result of acute or chronic myocardial ischemia caused by the mismatch in oxygen demand and oxygen supply (19). MI is defined as “myocardial cell death due to pathologically prolonged ischemia”. Research models of infarction and myocardial ischemia are critical for investigating the acute and chronic pathobiological and pathophysiological processes in myocardial ischemia, as well as developing and optimizing future treatments (20). Animal models must meet specific requirements for testing cardioprotective treatments for MI. Animal models are very useful in understanding the underlying pathophysiology and progression of ischemia to MI and unblocking clinical studies. Preclinical research contributes to the development of new strategies for the diagnosis, prevention, and treatment of MI, as well as their

implementation in clinical settings (21). Currently, MI models can be split into two types. The first is an acute model, while the second is chronic. The acute model is often created either by coronary artery ligation or by medication induction. Both occlude the bloodstream, resulting in the pathological process of MI. However, none of these methodologies incorporate the pathological process of atherosclerosis development, which is the foundation of a true acute MI (22).

Surgical Ligation Model of Acute MI

The most common surgical technique for acute MI is closure of the left anterior descending coronary artery. Ligating different portions of the coronary artery might cause MI. Johns and Olson (23) established this approach in 1954, and with a few modifications, it is currently commonly employed in both small and large animals. The surgical process consists of multiple steps. Briefly, the animals are sedated and placed in the supine position. The left side of the sternum is incised laterally, as are the third and fourth intercostal muscles. The retractor separates the third and fourth ribs; the heart is revealed through squeezing; and the left anterior descending coronary artery is ligated with sterilized sutures. Electrocardiography is used to validate the process; ST segment elevation and white staining of the anterior wall of the left ventricle suggest the onset of MI. The main disadvantages of this model are the high death rate, postoperative infection, infarct size ranging from 4 to 59%, and the requirement for professional hands and an artificial ventilator (24,25).

Chemical Models of Acute MI

Isoproterenol-Induced MI Model

Isoproterenol (isoprenaline, ISO) is a synthetic sympathomimetic catecholamine. Although it is very similar in structure to adrenaline, it only stimulates β1 and β2 receptors and does not affect α receptors at all. It is the first and widely used agent to experimentally induce MI in rats (26,27). Rats with acute MI caused by ISO provide a well-established, non-surgical animal model (28). Compared to the surgical model, this one has a number of benefits, including low mortality, ease of use, non-surgical approach, and consequently no risk of post-operative infection. This paradigm works best with rats, although it has also been observed to work with mice and rabbits, among other species (29,30). The most advantageous aspect of the usability of ISO is that it has been stated that high doses of rats overlap with all biochemical, physiopathological, and histopathological changes of heart attack in humans, and therefore the ISO-induced heart attack model is well-standardized. This model is frequently used to investigate the beneficial effects of many drugs or their effects on cardiac functions (31). ISO administration is usually administered on the last two days of the study, regardless of the duration of the study. MI in rats is induced by subcutaneous injection of 65-150 mg/kg ISO hydrochloride dissolved in saline (26,29,32). Reactive oxygen species (ROS) are produced when ISO is oxidized. ROS modify membrane permeability, raise levels of cardiac-specific enzymes, cholesterol, and low-density lipoprotein, and lower levels of endogenous antioxidant enzymes (26,33). Potential pathways of ISO-induced MI include oxidative stress, ischemia, intracellular calcium loading, metabolic modifications, and changes in electrolyte concentration (34,35).

Adriamycin (Doxorubicin)-Induced MI Model

Adriamycin is a broad-spectrum anticancer medication used to treat hematologic malignancies and a variety of solid cancers. Adriamycin's primary side effects are cardiomyopathy and HF. According to studies, oxidative stress is a key factor in the development of adriamycin cardiotoxicity (36). Cytotoxic and cytostatic mechanisms of action of doxorubicin include topoisomerase II inhibition, non-radical-dependent mechanisms such as binding of doxorubicin-iron complex to DNA and interaction of DNA base pairs with the drug, and DNA damage by free radical production (37). Numerous additional mechanisms have been proposed as adriamycin's modes of action. Numerous investigations have documented changes in calcium metabolism following doxorubicin treatment, primarily in the area of calcium excess. Increased intracellular calcium, calcium buildup in the ventricular myocardium, calcium inclusions in the mitochondria, abnormalities in calcium transport in cardiac tissue, and modifications to the sarcoplasmic reticulum's ability to release calcium through effects on the Ca++-ATPase and Ca++ release channel are some of these changes. HF may cause calcium to build up inside heart cells, therefore the increase in calcium levels that have been seen is more likely a result of the action of adriamycin than a cause (38). Rats administered adriamycin are often used in research to understand the mechanism of cardiotoxicity and to prevent it. Adriamycin administered to rats at 2 mg/kg/week for 12 weeks causes decreased blood pressure and cardiac output, and the development of pleural effusion, ascites, and liver congestion. The advantage of this model is that it is simple, noninvasive, economical, and develops quickly (36).

Adrenaline-Induced Myocardial Infarction Models

Also known as epinephrine, adrenaline is primarily a stress hormone produced by the adrenal glands and released into the bloodstream. It also has medical uses, including the treatment of cardiac arrest, allergic reactions, and asthma. However, it has been shown that high doses of adrenaline can increase the formation of ROS and reactive nitrogen species (RNS), leading to tissue damage (39). MI induced by adrenaline in rats is considered a reliable experimental model for studying the cardioprotective effects of drugs (2). Additionally, it has been discovered that adrenaline promotes lipid peroxidation and depletes cellular antioxidants as a contributing factor to MI (40). When adrenaline is administered, it is applied on the last two days of the study, similar to the ISO model. MI in rats is induced by subcutaneous injection of 1 mg/kg adrenaline dissolved in physiological saline. At the end of the study, changes in the ST segment on electrocardiography as well as alterations in CK-MB, cTn-T, and cTn-I levels are observed. Moreover, increases in oxidative stress parameters such as MDA and total oxidative status are noted. Additionally, histopathological changes are observed (2).

MI Model Induced by Coronary Artery Embolization Method

In the coronary artery embolization method, the microsphere that causes intracoronary embolization is created by intracoronary injection of agarose or polystyrene beads or autogenous blood carrying thrombin or fibrinogen (24,41). This method is mostly preferred in large animal models. This approach was developed by

Sabbah et al. (42). It was created by applying embolization with a catheter 3-9 times at different times for 1-3 weeks, using a closed ribcage model on dogs.

Coronary artery embolization is induced percutaneously. For this reason, the risk of serious inflammation observed after surgical interventions such as thoracotomy is reduced. In addition, this model resembles the clinical conditions of patients with HF and acute coronary syndrome in whom atherosclerotic embolization and thrombolytic debris have entered the coronary microcirculation. The factor that limits the embolization method is the uncertainty of the area of coronary artery occlusion and whether it is in the desired location (24).

MI Model Induced by Cryonecrosis Method

This pattern is induced by cryosurgery. After intercostal thoracotomy, it was created by using a 0.18x1.2 cm^2 liquid nitrogen probe in the left ventricle 15 times for 20 minutes. However, with the cryodamage method, transmural lesion formation and therefore fibrosis may not always occur and aneurysm formation may not be observed. This model has generally been applied to rats and rabbits (24,43). The model is highly reproducible, easy to implement, and can be set up quickly and reliably. It produces a consistent transmural infarct lesion independent of coronary anatomy and eventually leads to HF. This method is particularly suitable for evaluating innovative pharmacological and tissue engineering-based strategies and studying the remodeling process (2).

Electrically-Induced Myocardial Infarction

The use of rodent MI models provides a fundamental basis for studies investigating MI processes and how they can be treated. The experimental MI model created by electrical stimulation is performed with echocardiography support (44,45). The advantages of this model include being minimally invasive in mice and providing high repeatability. Its disadvantages include requiring expertise in intervention and imaging, as well as the high cost of equipment. The anesthetized mouse is positioned in a supine position on the imaging platform. Subsequently, the mouse's legs are spread and secured with a band. The ventral neck area of the mouse is shaved and the shaved area is disinfected with a 10% povidone-iodine solution (2). The left anterior descending artery (LAD) is evaluated using high-frequency ultrasound. A neutral electrode is attached to the mouse's right leg. Then, a micro-manipulator-controlled monopolar needle is slowly inserted into the closed chest cavity. The needle is gradually directed towards the targeted area. While the needle is on the LAD, an electrosurgical unit is used to coagulate the area with electricity. Subsequently, the needle is slowly withdrawn. The formation of MI or occlusion, meaning the absence of blood flow distal to the occlusion, akinesia in the affected part of the left ventricle, and typical electrocardiography changes within seconds confirm the occlusion. Cardiac morphological changes are evaluated with electrocardiographic and echocardiographic parameters along with cTn-T or cTn-I (2).

MI Model Induced by Hydraulic Occluder and Ameroid Generator Methods

This method is used to occlude all or part of the coronary arterial branches, especially in large animal models. Therefore, these methods are suitable for the coronary stenosis model required for inducing MI and HF and for examining myocardium hibernation (27,46,47,55,56). A left anterolateral thoracotomy is required for occluder implantation. Following the pericardial incision, the LAD branch is dissected, and the hydraulic occluder is then positioned around the vessel. After that, the hydraulic occluder is inflated to produce either a full or partial occlusion. To ascertain the extent of the obstruction and document the flow rate in the LAD, an ultrasonic flow probe is positioned distal to the obstruction (24,47).

The ameroid constrictor is implanted using the same technique, but a different mechanism is used to apply the obstruction. Because casein polymeric material is hygroscopic, the ring surrounding the vein gradually narrows at body temperature. The ameroid constrictor has been employed in investigations involving big animal models of MI, just like the hydrolytic occluder (24,47).

MI Model Induced by Coiling/Gelfoam Methods

In this method, after the carotid artery is dissected and exposed, the coils are placed into the LAD. Gelfoam sponges are placed inside the coils to completely close the coronary artery (48,49). Coils and sponges are also placed at the source of the second diagonal artery. This method is a technique that eliminates suturing around diagonal branches and thoracotomy. It may induce inflammation and formation of collateral circulation after surgical ligation with sutures. The development of platinum coils in harmony with magnetic fields has facilitated the method of occlusion of the coronary artery with a percutaneous catheter (24).

MI Model Induced by the Cauterization Method

The first starting point of this method, also known as burning, is the MI model created with the use of a green laser (50). Briefly, the cauterization method was developed by being inspired by and modifying this model; 4-5. A one cm incision is made between the ribs after the skin is opened in the dorsoventral direction, the pectoral muscles are opened with the help of a retractor without cutting, and before the heart is taken out, slight pressure is applied to the rib cage to compress the heart, and cauterization is applied to the same point three times to induce MI from the distal end of the left coronary anterior descending artery extending along the anterior of the heart. The application is done once. The most important advantage of this method over ligation is that the heart is not removed during the surgical intervention and therefore there is no need for intubation.

Models of Chronic Myocardial Infarction

The chronic coronary artery disease (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. The high-fat diet method involves feeding the experimental animals with rich cholesterol foods for a relatively long time. It induces hyperlipidemia, atherosclerosis, and sclerotic plaques, which result in stenosis in the blood vessels 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 preparing the model and the degree of ischemia is also difficult to control. At present, this method is successfully used with rats and

rabbits (22,51). A combination of medicines and ligation in conjunction with a high-fat diet can be used. The animal is first fed a high-fat or high-cholesterol diet for an extended length of time, resulting in lipid metabolic dysfunction and the progressive emergence of atherosclerosis. Myocardial ischemia can then be caused by a combination of medication injection and ligation. This technique allows for the convenient study of pathological changes and processes, as well as the treatment effect of medications on blood lipids, vascular lesions, and heart injury. The drug-induced effects are typically unstable, and ligation necessitates advanced surgical skills. Furthermore, this model cannot be employed in clinical settings to investigate autolysis recanalization, hence it is not optimal (22).

Animal Models of Heart Failure

HF is the number one cause of death worldwide. HF has a high death rate, with around 50% of patients dying within 5 years of diagnosis, which is higher than the mortality rate for most cancers (52). Furthermore, the prevalence of HF in industrialized nations is rising, resulting in a massive economic burden. The increase is due, at least in part, to improved treatment for acute MI, which has reduced mortality but not morbidity and is based on the number of surviving patients. Additional variables include an increased prevalence of comorbidities, which predispose to and accelerate the development of HF. As a result, there is an urgent need to change these risk factors and find new therapeutic approaches for HF patients (9).

To prevent and control HF caused by heart disease, it is vital to understand the pathophysiological mechanisms underlying these disorders and create innovative therapeutic techniques in response (5,8). Current treatments essentially halt the progression of this illness, highlighting the need for novel preventative and reparative therapy. The development of these innovative HF medicines necessitates testing of potential therapeutic techniques in relevant HF animal models (53).

Four clinical situations that can cause HF are described: Each will highlight essential characteristics of the clinical phenotype and recommend features of the clinical condition that should be included in an animal model designed to imitate the human state. Most animal models struggle to match the complexity of human illnesses that cause HF. HF models induced by myocardial ischemia: These are models created by coronary artery ligation and embolization (53,54). Tachycardia-induced HF model: Failure is created as a result of tachycardia with a fast atrial or ventricular pacemaker. In this model, due to technical difficulties, larger animals rather than small animals are generally used (54).

HF models created with pressure load and volume load: Pressure load with aortic valve stenosis and volume load with mitral valve insufficiency. HF models have been created with aortic stenosis in the supravalvular position in large animals such as cats, dogs, sheep, and pigs, and with transverse aortic stenosis in small animals such as mice. Mitral insufficiency and HF have been caused in dogs by cutting the chordae tendineae or by beta-adrenergic and angiotensin II pathways (53-55).

HF models are caused by hypertension and dilated, restrictive cardiomyopathy. Dilated cardiomyopathy is defined by ventricular dilation, systolic dysfunction, and diastolic filling abnormalities. The most important structural change is the increase in myocyte length and width. Additionally, interstitial fibrosis, decrease in extracellular matrix, progressive myocyte death, and decrease in capillary density are detected. In small and large animals, cardiomyopathy can be induced ischemically by surgical methods such as coronary artery ligation or damage, or by toxic agents (ISO, doxorubicin). Cardiomyopathy models can be used using spontaneously hypertensive rats, which develop spontaneous cardiomyopathy as they age, or in some cases genetically (53).

CONCLUSION

To summarize, the use of animal models in cardiovascular disease research is critical for improving our understanding of the pathophysiology of heart illnesses and evaluating new treatment options. From small animal models like mice and rats, which have provided valuable insights into genetic and molecular mechanisms, to larger animal models such as canines, swine, and sheep, which offer more similarities to human cardiovascular anatomy and physiology; each model has its advantages and disadvantages. However, the careful selection and design of animal models that mirror the specific pathophysiological mechanisms and characteristics of heart diseases in humans are essential for gaining crucial information to advance our understanding of cardiovascular diseases. These models not only allow for the study of anatomical, physiological, and cellular changes in cardiac disorders but also serve as a platform for the development of new therapeutic methods and the assessment of treatment efficacy. By considering the genetic homogeneity or heterogeneity, anatomical and physiological attributes, availability of background data, and practicality of using the animal model in research, researchers must ensure that the selected model accurately reflects the physiological and pathophysiological aspects of human cardiovascular disease. As research in cardiovascular disease continues to evolve, the role of animal models remains paramount in providing valuable insights into the pathophysiology of HF and the testing of potential therapies and interventions. Therefore, the careful consideration and selection of appropriate animal models for cardiovascular disease research are crucial in developing preventative and ameliorative treatments for this significant global health concern.

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