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Review Article

Animal Research Section

Induction of Myocardial Infarction in Experimental Animals: A Review

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ABSTRACT

Myocardial Infarction (MI) is a major health problem worldwide. Animal models have been used extensively in scientific research. This was intended to help researchers to understand the underlying pathophysiology of MI, compensatory mechanisms involved and efficacy of treatment. Although, it is difficult to create necrosis similar to those found in human heart, various large and small animals were used to create experimental model of MI. Each of these animals and method of selection offers various advantages and disadvantages in relation to clinical studies. In the present review, we aim to highlight the different methods used to induce MI in experimental animals. These methods may be beneficial for academicians and researchers concerned with the treatment of MI.

Keywords: Coronary artery, Isoprenaline, Ligation, Myocardial infarction

INTRODUCTION

Cardiovascular Disease (CVD) is a global health problem with high mortality and morbidity rate. There were 17, 700, 000 deaths due to CVD as per World Health Organization reports in 2015 [1]. CVD includes hypertension, Ischaemic Heart Disease (IHD), arrhythmia, congestive heart disease, valvular heart disease, heart failure and stroke. IHD occurs due to an imbalance between coronary perfusion and oxygen demand leading to MI. It encompasses the various clinical spectrum from unstable angina to MI, depending on the severity of coronary occlusion [2]. It was estimated that 493,321 patients were admitted to National Health Service Hospital in the UK in 2012-2013 for IHD [3].

There is a need to study MI in order to enrich one's knowledge about its pathophysiology and find better therapeutic options. In order to understand MI better, there is a need to create effective animal models. Various methods have been tried in animal species [4], either by using chemical [5], open surgery [6] or closed-chest catheter method [7]. The main objective of the present review is to discuss the various methods used to induce MI in the animals. The knowledge of such methods would be beneficial for researchers in specifying treatments in the MI related experiments.

Myocardial Infarction (MI)

MI is defined as necrosis of the heart muscle cells which results after prolonged deprivation of oxygen supply [8]. As a result of the reduction in blood supply, limited oxygen and nutrient supply cannot fulfill the tissue demand. Hence, cardiomyocyte death occurs.

Structural Changes Occurring During MI

Following ischaemia, the remaining blood vessel becomes dilated and collateral vessel develops. The least collateral blood flow, the larger is the infarct size [9,10]. According to Snell, coronary arteries are functional end arteries and they are not able to provide adequate blood supply to the heart muscle if the large vessel is occluded [11]. However, according to other researchers, in one-third of patients with atherosclerotic lesions, sufficient coronary collateral circulations were functionally available to prevent the patients from myocardial ischemia during brief vascular occlusions [9].

Structural Differences between the Human and Animal Heart

Even though the macroscopic features of the animal heart resembles that of humans, there are few differences in the gross anatomy of the structures. Due to these dissimilarities, experimental result in animal study may be challenging to be extrapolated, without the human clinical trial [12]. In addition, these differences make it difficult to design good animal model to mimic the pathophysiology found in human MI [13].

The unique feature of the cardiac muscle cell in human and most animals is its poor capacity of regeneration. However, zebrafish, teleost fish and urodele amphibians are capable of heart regeneration after cardiomyocyte death [14]. It was reported that the scar tissue formation following cryoinjury induced-MI in the zebrafish heart was replaced with new myocardium [14].

The closer the size of the animals to humans, the more is the similarity of the heart [15]. The body weight bears an inverse relationship with the heart rate [12,15]. In larger animals like the whale, the heart rate is 10 beats/min [16] while in a small animal like mouse, the heart rate can reach up to 800 beats/min [15].

Various patterns of collateral coronary network are observed in the animal species. These include guinea pig, cat and dog. They have good sizeable collateral coronary blood flow [12]. Hence, infarction does not occur after hours of coronary occlusion in the guinea pig [10]. In contrast, in animals such as rat, rabbit, pigs and non-human primates, there is sparse collateral coronary circulation. It was estimated that about 50% of ischaemic cardiomyocyte became necrotic after 34 minutes of coronary artery occlusion as reported in the rabbits [17]. The pig is also vulnerable to ischemia as the infarction develops 20-35 minutes after ischaemia and it takes 60 minutes for the anterior left ventricular wall to become completely infarcted [18]. Even though primates such as humans, monkeys and baboons have sparse collateral coronary blood flow, the development of infarction was gradually slow when compared to rats, rabbits and pigs [19,20].

Methods used to Induce MI in Animal Model [Table/Fig-1]

Chemical agent

Isoprenaline: Isoprenaline-induced MI is a simple, fast and less complicated method which is used to induce MI in the animal model. This technique offers indirect approach to produce MI as open surgery or thoracotomy is not required. Isoprenaline is a synthetic sympathomimetic catecholamine which produces 'infarct-like' myocardial necrosis resembling human myocardial infarction [21].

Isoprenaline acts non-selectively on β1 and β2 receptors. β1 receptors present predominantly on the heart, thus its stimulation leads to positive chronotropic, dromotropic and inotropic effect [22]. Upon administration of isoprenaline, ischaemia occurs due to the imbalance between cardiac stimulation and decreased coronary blood flow due to its depressor effect on circulation. Isoprenaline oxidation products are also believed to be involved in the myocardial damage [21].

Isoprenaline exhibits cardiotoxic lesions even at low dose [5] far below the level of the lethal dose [21]. The lesions produced are dose-dependent [5]. Low dose isoprenaline (32μg/kg) show abnormal histopathological changes as early as three hours post-injection [5]. Moderate dose isoprenaline (85mg/kg) shows significant alteration in biochemical parameters and moderate necrosis in the heart [23]. The myocardial injury becomes more extensive with higher dose of isoprenaline [24].

Isoprenaline produces infarct-like lesion similar to human MI [25]. Isoprenaline causes changes in the hemodynamic, biochemical, histopathological and oxidative stress markers [26]. Histopathological changes can be seen in subendocardial layer, myocardium of the apex, left ventricle, papillary muscle and interventricular septum [5,27].

Isoprenaline-induced MI is simple to execute. It can be administered subcutaneously [5], intraperitoneally [28] or intravenously [29]. However, these different methods of administration affect the drug metabolism and its conversion into inactive metabolites. According to previous researchers, the serum level of cardiac troponin was higher when isoprenaline was given subcutaneously compared to animal injected through intraperitoneal method [30]. This suggests that the route of administration affects the metabolism of the drug [30].

Isoprenaline-induced MI method has been used widely in the research on the protective effect of the natural product that can prevent myocardial necrosis damage [31] in the animal likes mice [32], rats [26], and rabbits [28]. In order to evaluate cardioprotective effect of natural product, isoprenaline is given 85 mg/kg on two consecutive days in mice and rats to produce MI [33]. According to an earlier research, the rabbits were induced with 3 mg/kg of isoprenaline injected intraperitoneally once prior to sacrifice [28]. Single dose of isoprenaline was enough to produce infarct-like necrosis in the heart but with repeated doses, the myocardial injury became more extensive [32].

Coronary Artery Ligation

Coronary artery ligation provides precise timing, location and extent of the coronary event due to direct visualisation and observation of the procedure and targeted area of infarct [4,6]. The procedure is initiated with administration of an anaesthetic agent to the animal, followed by securing the airway with the mechanical ventilator. The skin on the left side of the chest is incised, the muscles reflected and left thoracotomy is performed. The heart is rapidly exteriorized and specific site for ligation identified. The artery is then ligated with suture [34].

There are various approaches which have been introduced to ligate the coronary artery. If Left Coronary Artery (LCA) or proximal part of left anterior descending branch of the Left Coronary Artery (LAD) near its origin, which emerged from conus arteriosus and left auricle are ligated, large MI is produced with 100% mortality rate, with more than 65% of infarction occurring at the left ventricle [35]. Ligation of the segment of LAD at 2 mm lower than the tip of the left auricle is the most preferred site to induce MI in animals [6]. This artery is also a predominant site for occurrence of atherosclerosis [36]. Permanent occlusion of LAD produces infarction in the antero-apical and lateral wall of the left ventricle and anterior interventricular septum and also global impairment of left ventricular function [37]. Immediately after ligation of the artery, the ischaemic myocardium become pale in colour and abnormal ECG changes could be detected [4].

In the small animals like mice, identification and ligation of LAD is difficult to be conducted as the coronary arteries lay within the myocardium, not on the epicardial surface. Furthermore, the same red color of coronary arteries and myocardium make them difficult to be distinguished. Application of soft pressure at the apex was required to induce slight paleness of the myocardium [38].

Modification in the method of coronary artery ligation has been made to allow the study of reperfusion in the preclinical research. In human MI, myocardial reperfusion is performed to restore the balance between oxygen supply and myocardial demand, either by fibrinolytic therapy or Percutaneous Coronary Intervention (PCI). Timely reperfusion of the coronary artery after myocardial infarction is important to salvage the viable myocardium, limit infarct size, preserve LV systolic function and prevent the onset of heart failure [39]. However, with increasing duration and severity of ischemia, reperfusion of an ischemic area results in myocardial cell necrosis [40]. Thus, reperfusion injury is a term referring to the occurrence of tissue damage when blood supply return after the period of ischaemia [40].

To produce a reperfusion injury model, temporary occlusion of LAD is performed. It can be done by tying slipknot over the LAD [37]. After a certain period of time, the slipknot is released to allow the blood flow through the previously occluded artery. Hanging weight system is another alternative for an immediate release of coronary occlusion or reperfusion to avoid tissue trauma which can be obtained during manipulation of the knot [41].

Even though open-chest surgical ligation of coronary artery offers direct access to the heart, there are many disadvantages related to surgical operation such as complicated surgical procedure, anaesthetic complications, long operative times and low success rate [34]. Furthermore, the surgical procedure itself affects the whole balance of bodily function and modifies local and systemic immunological and inflammatory responses [4].

Closed-Chest Method to Induce Myocardial Infarction

In order to avoid complications related to the invasive procedure of open thoracotomy in the surgical open chest, percutaneous catheter method is introduced. This method is more suitable for large animals [7,42].

Coronary Artery Embolization

Percutaneous intracoronary embolization technique is a method to induce myocardial ischemia by catheterization of the coronary artery with the insertion of material into the coronary artery to form a thrombus. This model closely resembles human course of atherosclerotic disease superimposed by thrombus formation during MI event [7,42]. It offers minimal invasive method as no procedure of thoracotomy and pericardium incision is involved. However, this method requires anticoagulant therapy to prevent blood clot formation during instrumentation [43] and an anti-arrhythmic protocol to prevent arrhythmia and ventricular fibrillation [44].

Various materials have been inserted into the coronary artery for embolization such as sponge foam [44], various type of coils [4,7,45], polystyrene microspheres [43], alcohol injection [7] balloon catheter [45]. Sponge foam is easily available and inexpensive. The sponge foam is cut into small pieces of 5-7 mm of diameter. The fragmented sponge foam is placed over the wire and pushed into the targeted artery with the assistance of partially inflated balloon catheter. The mechanical obstruction is confirmed via angiography. Then the wire and balloon catheter are removed [44]. Delay ST-segment elevation of ECG may be observed 15 minutes after embolization [4].

The challenge in the percutaneous technique is the difficulty to control the exact location, length and duration of the coronary artery occlusion, and the overall volume of myocardial necrosis [4]. Occlusion of the proximal part of LAD resulted in severe heart failure, ventricular fibrillation with massive infarct, while embolization

of distal part of LAD causes the disturbance of atrioventricular conduction system [7]. Researchers suggested that the reliable area for inducing infarction with 25% decrease in LV ejection fraction is in the middle of the right coronary artery and circumflex coronary artery [7]. Another challenge in percutaneous technique is that it requires advanced technical skills and highly trained personnel to manipulate the catheter for deployment of the material for embolization [7].

Balloon Catheter

Balloon catheterization is usually conducted percutaneously. The balloon is inflated to produce coronary occlusion at the specific site and with deflation of the balloon; it simulates the ischaemia-reperfusion model. However, researchers have improvised this method to be used in the small animals for ischaemic reperfusion injury study. Instead of insertion of the balloon catheter into the coronary lumen, the balloon catheter is tied along with the coronary artery. Therefore, this method requires open surgery. Once the LAD is identified, the deflated balloon is tied loosely with the coronary artery. The ischaemia is induced when the balloon is inflated, and the return of perfusion is obtained when the balloon is deflated [46].

Ameroid Constrictor

Ameroid constrictor is a ring-like structure, made of a stainless steel, titanium or plastic [47]. It consists of casein material encased within the ring. This casein material is hygroscopic in nature [48]. Therefore, when the ameroid constrictor is placed around the coronary artery, it absorbs the surrounding fluid causing gradual narrowing of the lumen of the coronary artery it surrounds. The rate of narrowing of the lumen is accelerated within first two weeks, and then the rate of stenosis is slower until complete occlusion occurs. It is inserted into the desired place either through open chest method [49] or close-chest method with the aid of catheter [50]. The significant abnormal ECG changes are observed later than six hours after the procedure [50]. Due to its gradual occlusion that mimics chronic myocardial infarction, it enables the development of the collateral arterial supply [49]. This gradual occlusion can also be achieved by using hydraulic occluder [51].

Cryoinjury Induced Myocardial Infarction

Cryoinjury is another method used to induce MI. This method has been used in various animals such as zebrafish [14], mouse [52], rat [53] and pig [49]. According to Van Den Bos EJ et al., this is an ideal model used for the assessment of therapeutic intervention to restore cardiac function or cardiac regeneration after a case of MI [52].

Left chest incision is made following administration of anaesthetic agents. After left thoracotomy is performed, cryoprobe which has been precooled with liquid nitrogen is applied to the anterior left ventricular wall for few seconds. Therefore, anterior myocardial infarct occurs with modest adverse remodeling [52]. Van Den Bos EJ et al., compared the outcome of the myocardial injury produced by cryoinjury with the coronary artery ligation method [52]. He concluded that both showed the similar loss of contractility and diastolic dysfunction, however, more modest LV remodeling observed in the cryoinjury model with no overt heart failure. No overt heart failure is seen due to a small necrotic lesion of disc-shaped, induced by the cryoprobe. The lesion produced has similar cellular patterns of coagulation necrosis of myocardial infarction. Thus, it is a suitable model used to demonstrate myocardial repair [53].

The pathophysiology of MI in the cryoinjury method is different from other methods because acute cell death occurs following the cryoinjury without concomitant ischemia. It is due to mechanical forces induced by formation of ice crystals in the intra and extracellular space and in the vasculature [52]. This method has been used for research on intracardiac cell transplantation for myocardial repair [53]. It is because the transplanted cell is easily injected at its well-defined locations and presence of vascular reperfusion is beneficial for the cellular repair [52].

Surgical and Interventional Methods used to Induce MI in Different Systems of the Body:

Surgical Method

A method used to induce myocardial infarction also recapitulated in the research related to an intestinal ischemic injury. Intestinal ischemic injury model is produced to mimic a clinical condition in which there is deprivation of intestinal blood flow occurring during acute mesenteric ischemia, necrotizing enterocolitis or volvulus. This model is used to study the pathophysiology of ischemia. In this model, Superior Mesenteric Artery is either ligated [54] or embolized [55].

Interventional Method:

Ameroid Constrictor Method

Ameroid constrictor has been used in surgical management in a dog with a single portosystemic shunt. Ameroid constrictor is preferred as it produces gradual occlusion of the single extrahepatic vessel. It is important to allow development of collateral shunting vessel prior to the appearance of portal hypertension [56]. According to Murphy, surgical occlusion of the single extrahepatic portosystemic shunt with the ameroid constrictor is as effective as ligation method with the advantage of shortening of operating time and reduce complication related to ligation of shunting vessel [56].

Hydraulic Occluder Method

Hydraulic occluder has been reported to be effective to treat refractory urinary incontinence in animals like the cat [57] and dog [58]. Apart from that, it is also used in the treatment of congenital portosystemic shunt as it can offer gradual occlusion to the shunting vessel [59].

Method	Advantages	Disadvantages
Isoprenaline	Simple technique [32] Non-surgical method, non-invasive [32] High success rate [32] Low mortality rate [32]	Indirect method - visualisation of the effect on the targeted area is impossible during the procedure (32)
Coronary artery ligation	Precise control of site of occlusion via direct observation on the ligated artery [4] Able to control exact location and extent of the infarct area Suitable for small and large animals [37,49]	High mortality rate [6] Require artificial ventilator [6] Surgical and anaesthetic related complication [6]
Intracoronary embolization	Minimally invasive technique [7] Non-surgical method [7] Suitable for large animal [7,42]	Difficult to control exact location, length and duration of coronary ligation [7] Require artificial ventilator, require advanced method, expensive equipment and highly trained personnel to manipulate the catheter [7] Require anti-arrhythmic protocol [43]
Ameroid contrictor	Gradual occlusion of the coronary artery [49] Study on development of collateral artery [49]	May require open thoracotomy [49]
Cryoinjury	Suitable for research on study of cell transplantation for myocardial repair, heart regeneration and cellular remodeling [14]	Require open thoracotomy [49]

[Table/Fig-1]: Summary of advantages and disadvantages of various methods used to induce MI in animals.

CONCLUSION

Many animal models were designed to mimic clinical condition related to cardiovascular disease. A good animal model must be reproducible, able to provide consistent injury and can be translated to the human clinical condition. As per authors' review of literature, no statistical data has shown the best method to study all aspect of MI nor the most commonly used method to induce MI. Each method offers a different approach to induce ischaemia. For instance, occlusion of LAD, isoprenaline and cryoinjury are methods suitable to mimic acute MI, while ameroid constrictor and hydraulic occluder are more appropriate to study the effect of MI. To conduct MI in small animal, occlusion of LAD, isoprenaline, cryoinjury is the option of choice, whereas, for the large animal, occlusion of LAD, coronary artery embolization, balloon catheterization and ameroid constrictor are the list of selection. However, to study the effect of drug or natural product on MI, isoprenaline is the most commonly used method to induce MI. It is easy to execute. As isoprenaline acts non-selectively on β1 and β2 receptor, isoprenaline might as well affects other systems such as central nervous system, gastrointestinal, endocrine and metabolic system. Future improvement of isoprenaline is required to ensure it acts solely on target organ. Coronary ligation of LAD is also widely used in the experimental animals. However, the technique for thoracotomy, severity of occlusion as well as the agent of anaesthesia and technique for ventilation should be improvised to minimise the complication related to surgical procedure and anaesthesia. Perhaps in future, improvement is needed in the methods to induce MI as it would help researchers immensely in the cardiovascular-related field.

REFERENCES

[1] World Health Organization. Cardiovascular disease (CVDs): Fact sheet 2017 (released May 2017). http://www.who.int/mediacentre/factsheets/fs317/en/ [accessed April 10, 2018].
[2] Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 10th ed. Pennyslyvania: ElSevier; 2018.
[3] Bhatnagar P, Wickramasinghe K, William J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in UK 2014. Heart. 2015;101(15):1182-89.
[4] Katsanos K, Mitsos S, Koletsis E, Bravou V, Karnabatidis D, Kolonitsiou F, et al. Transauricular embolization of the rabbit coronary artery for experimental myocardial infarction: comparison of a minimally invasive closed-chest model with open-chest surgery. J Cardiothorac Surg. 2012;7:16.
[5] Zhang J, Knapton A, Lipshultz SE, Weaver JL, Herman EH. Isoproterenol-induced cardiotoxicity in Sprague-Dawley rats: correlation of reversible and irreversible myocardial injury with release of cardiac troponin t and roles of inos in myocardial injury. Toxicol Pathol. 2008;36(2):277–78.
[6] Xu Z, Alloush J, Beck E, Weisleder N. A murine model of myocardial ischemia-reperfusion injury through ligation of the left anterior descending artery. J Vis Exp. 2014;(86).
[7] Isorni MA, Casanova A, Piquet J, Bellamy V, Pignon C, Puymirat E, Menasche P. Comparative analysis of methods to induce myocardial infarction in a closed-chest rabbit model. Biomed Res Int. 2015;2015:893051.
[8] Zambahari R, Rajadurai J, Fong A, Hooi CG, Salleh NA, Ismail O, et al. clinical practice guideline management of acute ST Segment Elevation Myocardial Infarction (STEMI), 3rd ed. Purajaya: Ministry of Health Malaysia; 2014.
[9] Seiler C. The human coronary collateral circulation. Heart. 2003;89:1352–57.
[10] Heusch G. The coronary circulation as a target of cardioprotection. Circ Res. 2016;118:1643–58.
[11] Snell RS. Clinical Anatomy by Regions, 9th ed. Philadeplhia: Lippincott Williams & Wilkins; 2012.
[12] Ibáñez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. J Am Coll Cardiol. 2015;65(14):1454–71.
[13] Bracken MB. Why animal studies are often poor predictors of human reactions to exposure. J R Soc Med. 2009;102(3):120–22.
[14] Chablais F, Veit J, Rainer G, Jaźwińska A. The zebrafish heart regenerates after cryoinjury-induced myocardial infarction. BMC Dev Biol. 2011;11:21.
[15] Milani-Nejad N, Janssen PML. Small and large animal models in cardiac contraction research: advantages and disadvantages. Pharmacol Ther. 2014;141(3):235–49.
[16] Race GJ, Edwards WLJ, Halden ER, Wilson HE, Luibel FJ. A large whale heart. Circulation.1959;19(6):928–32.
[17] Miura T, Downey JM, Ooiwa H, Ogawa S, Adachi T, Noto T, Shizukuda Y, Iimura O. Progression of myocardial infarction in a collateral flow deficient species. Jpn Heart J. 1978;30(5):695–708.
[18] Pich S, Klein HH, Lindert S, Nebendahl K, Kreuzer H. Cell death in ischemic, reperfused porcine hearts: a histochemical and functional study. Basic Res Cardiol. 1988;83(5):550–59.
[19] Hedström E, Engblom H, Frogner F, Åström-Olsson K, Öhlin H, Jovinge S, Arheden H. Infarct evolution in man studied in patients with first-time coronary occlusion in comparison to different species - implications for assessment of myocardial salvage. J Cardiovasc Magn Reson. 2009;11(1):38.
[20] Yang XM, Liu Y, Liu Y, Tandon N, Kambayashi J, Downey JM, Cohen MV. Attenuation of infarction in cynomolgus monkeys: preconditioning and postconditioning. Basic Res Cardiol. 2010;105(1):119–28.
[21] Rona G. Catecholamine cardiotoxicity. J Mol Cell Cardiol. 1985;17(4):291–306.
[22] Shukla AC, Steven JM, Jr FXM. Cardiac Physiology and Pharmacology. In: A Pract. Anaesth. Infants Child, Philadeplhia: Saunder; 2009, Pp. 361–395.
[23] Peer PA, Trivedi PC, Nigade PB, Ghaisas MM, Deshpande AD, Goel RK. Cardioprotective effect of Azadirachta indica A. Juss. on isoprenaline induced myocardial. Int J Cardiol. 2008;126(1):123-26.
[24] Ribeiro D, Buttros J, Oshima C, Bergamaschi C, Campos R. Ascorbic acid prevents acute myocardial infarction induced by Isoproterenol in rats: role of nitric oxide synthase production. J Mol Histol. 2009;40(2):99-105.
[25] Rona G, Kahn DS, Chappel CL. Study on the healing of cardiac necrosis in the rat. Am J Pathol. 1961;39(4):473–89.
[26] Shikalgar TS, Naikwade NS. Evaluation of cardioprotective activity of fulvic acid against isoproterenol induced oxidative damage in rat myocardium. Int Res J Pharm. 2018;9(1):71-80.
[27] Hasić S, Jadrić R, Kiseljaković E, Mornjaković Z, Winterhalter-Jadrić M. Troponin T And Histological characteristics of rat myocardial infarction induced by isoproterenol. Bosn J Basic Med Sci. 2007;7(73):212–17.
[28] Pinelli A, Trivulzio S, Tomasoni L, Brenna S, Bonacina E, Accinni R. Isoproterenol-induced myocardial infarction in rabbits. Protection by propranolol or labetalol: a proposed non-invasive procedure. Eur J Pharm Sci. 2004;23(3):277–85.
[29] Hoffbrand BI, Forsyth RP, Melmon KL. Dose-related effects of isoprenaline on the distribution of cardiac output and myocardial blood flow in conscious monkeys. Cardiovasc Res. 1973;7(5):664–69.
[30] Brady S, York M, Scudamore C, Williams T, Griffiths W, Turton J. Cardiac Troponin I in isoproterenol-induced cardiac injury in the hanover wistar rat: studies on low dose levels and routes of administration. Toxicol Pathol. 2010;38(2):287–91.
[31] Upaganlawa A, Gandhi H, Balaraman R. Isoproterenol induced myocardial infarction: protective role of natural products. J Pharmacol Toxicol. 2011;6(1):1–17.
[32] Brooks WW, Conrad CH. Isoproterenol-induced myocardial injury and diastolic dysfunction in mice: structural and functional correlates. Comp Med. 2009;59(4):339–43.
[33] Hassan MQ, Akhtar M, Ahmed S, Ahmad A, Najmi AK. Nigella sativa protects against isoproterenol-induced myocardial infarction by alleviating oxidative stress, biochemical alterations and histological damage. Asian Pac J Trop Biomed. 2017;7(4):294–99.
[34] Wang J, Bo H, Meng X, Wu Y, Bao Y, Li Y. A simple and fast experimental model of myocardial infarction in the mouse. Texas Hear Inst J. 2006;33(3):290–93.
[35] Yeap XY, Dehn S, Adelman J, Lipsitz J, Thorp EB. Quantitation of acute necrosis after experimental myocardial infarction. Methods Mol Biol. 2013;1004:115–33.
[36] Wasilewski J, Niedziela J, Osadnik T, Duszańska A, Sraga W, Desperak P, et al. Predominant location of coronary artery atherosclerosis in the left anterior descending artery. The impact of septal perforators and the myocardial bridging effect. Polish J Cardio-Thoracic Surg. 2015;12(4):379–85.
[37] Gao E, Lei YH, Shang X, Huang ZM, Zuo L, Boucher M, et al. A novel and efficient model of coronary artery ligation and myocardial infarction in the mouse. Circ Res. 2010;107(12):1445–53.
[38] Redel A, Jazbutyte V, Smul TM, Lange M, Eckle T, Eltzschig H, et al. Impact of ischemia and reperfusion times on myocardial infarct size in mice in vivo. Exp Biol Med. 2008;233(1):84–93.
[39] Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest. 2013;123(1):92–100.
[40] Verma S, Fedak PWM, Weisel RD, Butany J, Rao V, Maitland A, et al. Fundamentals of reperfusion injury for the clinical cardiologist. Circulation. 2002;105(20):2332–36.
[41] Eckle T, Grenz A, Köhler D, Redel A, Falk M, Rolauffs B, et al. Systematic evaluation of a novel model for cardiac ischemic preconditioning in mice. Am J Physiol Circ Physiol. 2006;291(5):H2533–40.
[42] Lukács E, Magyari B, Tóth L, Petrási Z, Repa I, Koller A, et al. Overview of large animal myocardial infarction models (review). Acta Physiol Hung. 2012;99(4):365–81.
[43] Hanes DW, Wong ML, Jenny Chang CW, Humphrey S, Grayson JK, Boyd ED, et al. Embolization of the first diagonal branch of the left anterior descending coronary artery as a porcine model of chronic trans-mural myocardial infarction. J Transl Med. 2015;13:187.
[44] Dariolli R, Takimura CK, Campos CA, Lemos PA, Krieger JE. Development of a closed-artery catheter-based myocardial infarction in pigs using sponge and lidocaine hydrochloride infusion to prevent irreversible ventricular fibrillation. Physiol Rep. 2014;2(8):e12121.
[45] Krombach GA, Kinzel S, Mahnken AH, Günther RW, Buecker A. Minimally invasive close-chest method for creating reperfused or occlusive myocardial infarction in swine. Invest Radiol. 2005;40(1):14–18.
[46] Hu F, Zhai N, Gao W, Wu P, Luo Y, Pan D, et al. Outer balloon ligation increases success rate of ischemia-reperfusion injury model in mice. PLoS One. 2016;11(12):e0167631.
[47] Keeran KJ, Jeffries KR, Zetts AD, Taylor J, Kozlov S, Hunt TJ. A chronic cardiac ischemia model in swine using an ameroid constrictor. J Vis Exp. 2017;(128).
[48] Klocke R, Tian W, Kuhlmann M, Nikol S. Surgical animal models of heart failure related to coronary heart disease. Cardiovasc Res. 2007;74(1):29–38.

[49] Hirano A, Fujita J, Kanazawa H, Kawaguchi S, Handa N, Yamada Y, et al. Cryoinjury-induced acute myocardial infarction model and ameroid constrictor-induced ischemic heart disease model in adult micro-mini pigs for preclinical studies. Transl Med Commun. 2017;2(1). doi:10.1186/s41231-017-0011-y.
[50] Nakhajavan FK, Shedrovilzky H, Goldberg H. Experimental myocardial infarction in dog description of a closed chest technique. Circulation. 1968;38:777–82.
[51] Cantyr J, Fallvollita J. Chronic hibernation and chronic stunning: A continuum. J Nucl Cardiol. 2000;7(5):509-27.
[52] Van Den Bos EJ, Mees BME, De Waard MC, De Crom R, Duncker DJ. A novel model of cryoinjury-induced myocardial infarction in the mouse: a comparison with coronary artery ligation. Am J Physiol Hear Circ Physiol. 2005;289:1291–300.
[53] Murry CE, Wiseman RW, Schwartz SM, Hauschka SD. Skeletal myoblast transplantation for repair of myocardial necrosis. J Clin Invest. 1996;98(11):2512–23.
[54] Gonzalez LM, Moeser AJ, Blikslager AT. Animal models of ischemia-reperfusion-induced intestinal injury: progress and promise for translational research. Am J Physiol Gastrointest Liver Physiol. 2015;308(2):G63-75.
[55] Acosta S, Nilsson TK, Malina J, Malina M. L-Lactate after embolization of the superior mesenteric artery. J Surg Res. 2007;143(2):320–28.
[56] Edwards R, Yousef Z, Rakhit R, Wright M, Rosenthal E, Redwood S, et al. A model of closed chest regional myocardial infarction in the rabbit: a clinically relevant in vivo assay system of post-infarction remodelling. Basic Res Cardiol. 2002;97(5):374-83.
[57] Wilson KE, Berent AC, Weisse CW. Use of a percutaneously controlled hydraulic occluder for treatment of refractory urinary incontinence in three female cats. J Am Vet Med Assoc. 2016;248(5):544-51.
[58] Currao RL, Berent AC, Weisse C, Fox P. Use of a percutaneously controlled urethral hydraulic occluder for treatment of refractory urinary incontinence in 18 female dogs. Vet Surg. 2013;42(4):440-47.
[59] Adin CA, Sereda CW, Thompson MS, Wheeler JL, Archer LL. Outcome associated with use of a percutaneously controlled hydraulic occluder for treatment of dogs with intrahepatic portosystemic shunts. J Am Vet Med Assoc. 2006;229(11):1749-55.

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