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Review

Limitations of the Use of Animal Models of Acute Myocardial Infarction for Experimental Studies of Vascular Cognitive Dysfunction: Brief Review

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Abstract: This brief review presents Russian and foreign models of acute myocardial infarction (AMI), which are used to gain new knowledge about the pathophysiology of the development of this disease, as well as to search for sensitive and specific biomarkers of AMI and associated pathologies, including vascular cognitive disorders. However, modeling vascular cognitive disorders associated with AMI is a challenging task. Re-searchers need to take into account the additive effect of ischemia of striated muscles (myocardium or skeletal muscles) and central anesthetics during the simulation of AMI in experimental animals.

Keywords: *fundamental cardiology; fundamental neurology; experiment; animal model; acute myocardial infarction; disease modeling; rat.*

1.Introduction

Acute myocardial infarction (AMI) is an acute injury (necrosis) of the myocardium due to ischemia [1]. AMI is one of the leading causes of death in the developed world [2, 3]. The prevalence of this disease is approaching 3 million people worldwide, while in the Russian Federation, the death rate from myocardial infarction amounted to 50.2 thousand people [4]. In recent years, methods of early diagnosis of AMI and comorbid conditions have been improved, which can play an important role in a personalized approach to its therapy and prognosis of outcomes [5]. Of great interest to Russian and foreign researchers is the problem of developing and introducing into real clinical practice new sensitive and specific biochemical and molecular biomarkers of AMI and vascular cognitive disorders associated with AMI [6, 7]. The most studied biomarkers of AMI that have found widespread use in clinical practice are cardiac troponins [8, 9]. The most studied biomarkers of AMI that have found widespread use in clinical practice are cardiac troponins [10], including vascular cognitive disorders. This explains the relevance of the search for new biomarkers of AMI and associated vascular cognitive disorders.

Since previously proposed and well-known serum and plasma biomarkers of AMI, such as: troponin test and muscle creatine kinase level [11], may increase only 12-24 hours after the development of acute ischemia, it is important to search for sensitive and specific early biomarkers of AMI in patients with acute coronary syndrome. However, to solve this problem, it is important to conduct exploratory and fundamental research in cardiology, including using an animal model of AMI. At the same time, comparing the results of fundamental research using different models of AMI [12, 13, 14, 15] and their translation

into clinical practice may be difficult due to the variability of the methodology for modeling this cardiovascular disease and the timing of blood and tissue samples from laboratory animals for their subsequent analysis and clinical interpretation of the data obtained in the aspect of the study of cellular and plasma biomarkers of associated vascular cognitive disorders.

The purpose of this brief review is to analyze research in the field of fundamental cardiology using methods of modeling AMI in experimental animals (rats).

2. Materials and Methods

English and Russian-language publications were searched in the databases PubMed, Springer, Web of Science, Clinical keys, Scopus, OxfordPress, Cochrain and e-Library. The search was conducted using keywords and phrases: fundamental cardiology; fundamental neurology; experiment; animal model; acute myocardial infarction; cognitive disorder; disease modeling; rat. Full-text articles published between January 2014 and January 2024 were analyzed. A total of 208 publications were analyzed, from which duplicate publications and publications with no access to the full-text version were excluded. In total, this brief review includes 7 animal models of AIM that meet the purpose and criteria of the search.

3. Results

Rats were used as an animal model of AMI in all analyzed publications. However, the modeling of AMI in rats varied in a wide range, including 4 minimally invasive models (ischemia of skeletal muscles of the hindlimb of a rat) [16, 17, 18, 19] and 4 invasive models (coronary artery ischemia) [20, 21, 22, 23]. On the one hand, when using invasive and minimally invasive models of AMI, researchers applied central methods, which could hypothetically affect the expression level of biochemical (muscle variant of creatine kinase, troponin test) [24] and molecular (circulating microRNAs) [25, 26] biomarkers of AMI and cognitive disorders [27]. On the other hand, the analyzed studies differed in the variability of the duration of experimental ischemia in the modeling of AMI, which can also affect the expression of the studied biochemical and molecular biomarkers of AMI and AMI-associated cognitive disorders, leading to a change in their level in peripheral blood.

3.1. Minimally Invasive Models of Acute Myocardial Infarction in Experimental Animals

Voronov D.A. et al. [16] proposed a three-level ligation of the arterial trunk of the hind limb of a rat with a non-absorbable suture material.

Methodology: The first ligature was applied to the external iliac artery. The second ligature was placed in the area of the common femoral artery directly under the inguinal ligament, and the third ligature was placed on the popliteal artery. A mandatory component of this experimental model of AMI was the excision and removal of a section of the peripheral artery between the second and third ligatures. An additional ligature was applied to the venous trunk of the rat's hind paw in order to ligate the femoral vein in its middle third.

Analgesia method: Not described.

Petrishchev N.N. et al. [17] proposed an alternative animal model of AMI based on ischemia of the hind limb of a rat using photochemical thrombosis of the femoral artery.

Methodology: An incision of the skin and underlying muscles was made with a scalpel in the area of the surface of the rat's left thigh (incision size ⌀2 cm). Then, a section of the femoral vein was freed from the surrounding soft tissues, which was dotted to administer a photosensitizer solution (Bengali pink A) in a single dose of 1.7 mg per 100 g of

weight of the experimental animal in dilution in 1 ml of 0.9% aqueous sodium chloride solution. Immediately after intravenous administration of the photosensitizer, an incision ⌀2 cm long was made in the area of the inner surface of the rat's right thigh. A section of the femoral artery 4 mm long was freed from the surrounding soft tissues, which was then ligated with a strip of opaque black plastic 3 mm wide, which made it possible to isolate the femoral vein and surrounding tissues from radiation. A diode laser with a wavelength of 532 nm and a power of 60 MW was used for photosensitization. The irradiation area of the femoral vein was 1 mm2, duration - 30 min. After the end of the photosensitization session, a strip of black plastic was removed and the wound on the hind leg was sutured. Experimental thrombosis of the femoral artery in all animals developed on average 15-20 minutes after the start of the photosensitization session against the background of intravenous administration of Bengal pink.

Analgesia method: central anesthesia with an aqueous solution of sodium thiopental (50 mg / kg weight of the experimental animal), which was administered intraperitoneally.

Waterman R.S. [18] used an animal model of AMI based on ischemia of skeletal muscles of the hind limb of a rat.

Methodology: Ischemia of skeletal muscles was achieved by ligation of the iliac artery to the inguinal fold. At the same time, the distal sections of the doped vessel were not removed. Additionally, two or three skin wounds with a maximum size of 4-5 mm were inflicted in this area with a scalpel.

Analgesia method: Not described.

Elmali N. et al. [19] developed an experimental model of AMI in rats based on ischemia of the skeletal muscles of the hind limb by local application of a tourniquet.

Methodology: A tourniquet was applied to the hindlimb of a rat with exposure for 4 hours. This ensured the cessation of blood flow through the main artery and acute local ischemia of muscle tissue. This AMI model can additionally allow the assessment of 4- and 8-hour reperfusion, which is of scientific interest for the study of both AMI biomarkers and reperfusion injuries.

Analgesia method: central intramuscular anesthesia with ketamine hydrochloride solutions at a dose of 30 mg / kg and xylazine hydrochloride at a dose of 2 mg / kg, which were injected into the anterior part of the rat's hind limb. To maintain anesthesia, 10 mg of ketamine was administered intramuscularly every 30-45 min.

3.2. Invasive Models of Acute Myocardial Infarction in Experimental Animals

Nevzorova V.A. et al. [20] proposed a method of myocardial ischemia by drug-induced coronary artery thrombosis.

Methodology: Under aseptic conditions, an incision of the skin of the chest was performed with a size of about 2 cm. The pectoral muscles were bred before the appearance of rib arches and intercostal muscles. Then, palpation of the apical impulse of the heart was performed and 0.25 ml of 1.5% vascular sclerosing drug ethoxysclerol was injected into the thickness of the myocardium of the anterior wall of the organ through the intercostal space. The drug was administered with an atraumatic needle with a triple silicone coating according to the original method. The triple silicone coating allowed the needle to enter the myocardium in the most gentle mode without destroying it. After suturing the skin, the suture was treated with chlorhexidine.

Analgesia method: central inhalation anesthesia with sevoran. The duration of the experiment did not exceed 3-5 minutes. 10 minutes after inhalation of sevoran vapors, the animal regained consciousness and motor activity.

Table 1. Animal models of acute myocardial infarction (rats)

Animal model	Description	References
	Ischemia of the muscles of the hind limb	
Modeling by Voronov	Three-level ligation of the arterial trunk of the posterior lower limb with fragment resection between the second and third ligatures in combination with ligation of the femoral vein in the middle third	[16]
Modeling by Petrishchev	Photochemical thrombosis of the femoral artery against the background of injection of Bengal pink solution into the femoral vein of the hind paw of an experimental animal.	[17]
Modeling by Waterman	Single-level ligation of the iliac artery to the level of the inguinal fold, followed by the application of two or three wounds on the skin of the hind limb of the experimental animal.	[18]
Modeling by Elmali	Single-level 4-hour local cessation of blood flow through the main artery of the hind limb of a rat by applying a tourniquet.	[19]
	Myocardial ischemia	
Modeling by Nevzorova	Drug-induced coronary artery thrombosis.	[20]
Modeling by Kogan	Single-level ligation of the coronary artery.	[21]
Modeling by Selya (modification by Nikulina)	Single-level ligation of the coronary artery.	[22, 23]

Kogan A.H. [21] developed an experimental model of AMI in rats based on open ligation of the coronary artery at the median or low vertebral level (the place of transition of the left edge of the cone to its base, where the left coronary artery deviates somewhat and goes steeply down to the apex of the heart).

Analgesia method: subcutaneous administration of a 5% hexenal solution calculated at 0.05 – 0.07 ml per 100 g of weight of an experimental animal, followed by placing the animal in a jar with ethyl ether vapor for anesthesia for 10 minutes.

Selye H. et al. [22] in 1960, he developed an experimental model of AMI in rats, which was modified by Nikulina N.A. et al. [23] in 2020.

Methodology: A pressure bandage was applied to the rat's abdomen. The skin was incised and separated from the underlying pectoral muscles, which were then sutured with a pouch. After that, the intercostal muscles were separated and the wound expanded. The pericardium was opening. Then the heart was brought out. A ligature was applied with an atraumatic needle of 110 mm (vicryl 5-0). The needle was inserted 1 mm below the edge of the left auricle, then through the thickness of the myocardium perpendicular to the axis of the heart. The needle exit was carried out through 3-4 mm, without going beyond the groove to the right parts of the heart. The ligature was tightened with 3 knots, the heart returned to the chest, and the wound dilator was removed. Simultaneously with the tightening of the pouch seam, air was removed from both sides by light pressure on the chest, the pneumothorax was eliminated, and the rat began to breathe. The pressure bandage was removed. Resuscitation measures were carried out by precardial impact to the chest from the front, indirect heart massage, and light atraumatic pulling of the animal by the tongue.

Analgesia method: the author's technique of Nikulina N.A. et al. [[23] by combining 1% sodium thiopental solution (40 mg/kg intraperitoneally) and 5% tramadol solution (0.03 ml/100 g, intramuscularly).

4. Discussion

In this brief review, 7 models of AMI in rodents were analyzed, of which 4 were invasive and required thoracotomy (Table 1). Central anesthetics and opioid analgesics were used for anesthesia. This explains the need to comply with the instructions in force in the Russian Federation on accounting for the storage and use of potent and narcotic drugs. Another limitation of the widespread use of invasive AMI models is the potential impact of the duration of general anesthesia, the central anesthetics themselves [28, 29, 30] and cardiac arrest during the experiment on serum levels of biochemical and molecular biomarkers of AMI.

The advantages of minimally invasive animal models of AIM (ischemia of skeletal muscles of the hindlimb in rats) were the simplicity of the experiment and the rejection of thoracotomy. These AMI models are of the greatest scientific interest for the study of circulating microRNAs as biomarkers of AMI and AMI-associated vascular cognitive disorders. Thus, it was previously shown that some AMI-sensitive microRNAs have a high level of expression in the myocardium and skeletal muscles (for example, miR-1, miR-133a/b, miR-208b, miR-486 and miR-499 [31, 32]). In addition, such animal models of AMI may be more preferable from the standpoint of bioethics [33].

5.Conclusion

Modeling vascular cognitive disorders associated with AMI is a challenging task. Researchers need to take into account the additive effect of ischemia of striated muscles (myocardium or skeletal muscles) and central anesthetics during the simulation of AMI in experimental animals.

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