Experimental Myocardium Infarction in Rats: Analysis of the Model

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Summary

One of the most often used strategies to study the physiopathological alterations caused by coronary occlusion is the use of the experimental infarction model in rats. Among other factors, this is due to the similarities in the physiopathological alterations that occur after the infarction in humans. One must consider, however, that this model has characteristics that can hinder the use as well as the interpretation of eventual outcomes. Thus, this review aims at analyzing the main characteristics of the experimental infarction model in rats, discussing the coronary occlusion technique, the consequences and the methods of morphological and functional assessment of the infarction and its clinical implications.

Introduction

The acute myocardial infarction (AMI) is defined as a focus of necrosis that results from low tissue perfusion, with signs and symptoms that are the consequence of the cardiac cell death.

It is estimated that this syndrome can occur in epidemic proportions worldwide. Few pathologies had their evolution altered so radically as the AMI, with an accentuated decrease in mortality due to the changes regarding its treatment in the last 30 years[1,2]. The change in the treatment was the result of advances obtained in the study of the pathogenesis of the AMI and its complications. This fact emphasizes the importance of a better understanding of the physiopathological mechanisms of the acute coronary syndromes.

One of the most often used models to study the physiopathological alterations caused by coronary occlusion is the experimental infarction model in rats. However, the model presents several particular characteristics that can make it difficult to handle. Thus, the objective of this review is to discuss the main methodological aspects related to the experimental infarction model in the rats.

Key Words

Myocardial infarction; animals, laboratory; rats; coronary occlusion.

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Method development

The experimental AMI model in rats due to left coronary occlusion was initially described by Heimburger in 1946[3]. With the passing time, the technique was progressively modified by Johns and Olson[4], Kaufman et al[5] and Seyle et al[6]. In the beginning of the 1980s, the method was introduced in Brazil at the School of Medicine of Botucatu[7], and from there it spread to other Services. In short, after the anesthesia, a left thoracotomy is performed, between the 4th and the 5th intercostal spaces. The heart is exteriorized through lateral compression of the chest and the left coronary artery is ligated with 5-0-size suture thread at approximately 2 mm from its origin, between the left atrium border and the pulmonary artery sulcus (Figure 1). Then, the heart is rapidly returned to the thoracic cavity, the lungs are expanded with positive ventilation with 100% oxygen and the surgical wound is closed [3-6]. The method described above has several advantages. First, the animals can be raised specifically for the protocols, at a lower cost than with larger animals. Second, the surgery is extremely fast, with a duration ranging from 2 to 5 minutes. Another aspect is that due to the rat metabolism characteristics, the phases involved in the infarction evolution such as necrosis, healing and remodeling occur rapidly, which decreases the time of study observation. Finally, the morphological and functional alterations caused by the infarction are similar to those found in humans[8,9].

Animals and surgery

The most often used rat strains are Wistar and Sprague-Dawley, depending on the Service and animals weighing 200 to 250g are usually used in the studies. In this weight range, a rat is considered a young adult, when its evolution phase is characterized by slow growth and presents lower surgical mortality than older animals. It is also recommended to use animals of the same sex, as this variable can be an important regulation factor of the cardiac adaptations in response to several stimuli[10,11].

Regarding the anesthesia, several agents have been used, and among them, inhalation agents such as ether and isoflurane, as these drugs are relatively inexpensive plus the advantage of having a short-term action, in addition to allowing the variation of anesthesia intensity during surgery[10].

Barbiturates or the association of ketamine chloride (50 mg/kg) and xylidine chloride (1mg/kg) are also frequently used via intraperitoneal or intramuscular routes. These agents are fast-acting and can produce anesthesia within 5 minutes. It is important to remember that the agents with short half-life are preferable to the long-action ones[10].

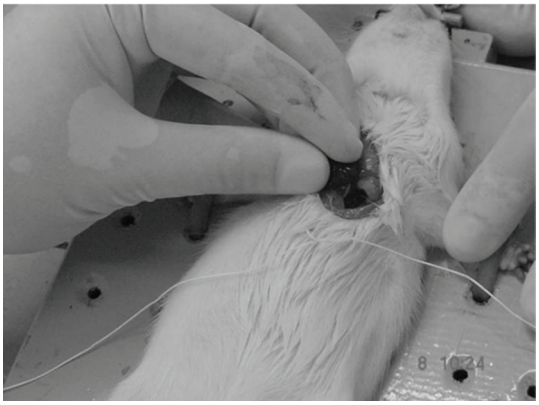

Figure 1 - Experimental infarction. Exteriorization of the heart for coronary suture at 2 mm from the origin, between the border of the left atrium and the pulmonary artery sulcus.

During the procedure, it is recommended that the animals be artificially ventilated, with oxygen supplementation. Therefore, the animals can be ventilated by nasal compression, with catheter, or be submitted to mechanical ventilation after orotracheal intubation with a number 16 catheter[10].

After the surgery, the most commonly used analgesic drugs are morphine, dipyrone or paracetamol. Another aspect is that the environmental conditions must be kept constant, as temperature variations, for instance, can increase the mortality after the infarction.

Mortality

The observed mortality within the first 24 hrs after surgery is usually 40 to 60%. Among the causes of death in this period are mainly the factors related to the surgical procedure, such as pneumothorax and respiratory depression as well as factors associated to the cardiac pump failure, such as acute pulmonary edema[10,12]. The main cause of death in this model is, however, the high prevalence of malignant arrhythmias, such as sustained ventricular tachycardia and ventricular fibrillation. Opitz and cols. found a mortality of 65% in the first 48 hours after the infarction. Through continuous monitoring, the authors demonstrated that 96% of the animals submitted to the AMI presented hundreds of episodes of ventricular tachycardia and at least 20 episodes of ventricular fibrillation. Additionally, two distinct periods of arrhythmia were demonstrated: the first period included the first 30 minutes after the coronary occlusion and the second, responsible for 65% of the deaths, included the period between 1.5 and 9 hours after the infarction[13].

Regarding the chronic period after the AMI, the mortality observed in this model is extremely variable, with the size of the infarction being the main determinant of this event. In this sense, Pfeffer et al[14], following infarcted animals for a period of one year, verified that for small (5 to 19.9% of the left ventricle), moderate (20 to 39.9%) and large infarctions (≥ 40%), the mortality rates were around 50%, 75% and 85%, respectively[14].

Aspects related to the size of the infarction

One of the most relevant aspects of this model is related to the size of the infarction. It is accepted that this parameter resulting from the coronary occlusion, in its proximal region, is not uniform, varying from 4% to 65%[12]. This fact is a consequence of the incapacity of occluding the coronary exactly at the same point in all animals, as well as of eventual anatomic variations among them. Thus, this model is not adequate for the verification of the reduction effect of infarct size through different interventions, as eventual differences in the infarction size might be inherent to the variability of the method. Consequently, it is recommended first the analysis of the risk area affected by the coronary artery ligation in a certain point, through the injection of dyes. Subsequently, starting from the risk area, the size of the final infarcted area is verified[15,16].

Another factor to be considered is the site of the occlusion of the coronary artery. When the occlusion occurs too close to the origin, there is the septal artery involvement and the size of the infarction can be higher than 65%. In this case, however, the mortality of the animals is 100%[12,14].

Another relevant characteristic is that, in this experimental model of AMI, the percentage of infarction at the apex is higher than that at the basis of the left ventricle. For this reason, the most often used method to determine the size of the infarction is the one that uses several transversal cuts. The size of the infarction is determined by the mean of all cuts. Different authors, however, have observed that the medial transversal cut of the left ventricle, between 5 and 6 mm from the apex, reflects the size of the infarction of the entire left ventricle[17,18]. Therefore, the use of this region alone would simplify the measurement of the infarction size.

Regarding the methods used to determine the infarction size, this variable has been assessed, preferentially, by 4 different methods: 1) measurement of the infarcted area in relation to the left ventricle area, determined by histology or planimetry; 2) histology with the measurement of the internal perimeter of the infarcted area in relation to the total perimeter of the cavity; 3) histology with the measurement of epicardial and endocardial circumferences of the infarcted and non-infarcted segments and 4) echocardiogram with the measurement of the internal perimeter of the infarcted region in relation to the total perimeter of the cavity.

The most often recommended method for determining the infarction size is the measurement of the epicardial and endocardial circumferences of the infarcted and non-infarcted segments (Figure 2)[12,14,19]. A potential limitation to the use of different techniques is, as mentioned before, the fact that the size of the infarction can vary, depending on the method used.

Regarding the measurement of the infarction size by the area, one must consider that, after the infarction, dynamic alterations occur in the infarcted segment as well as in the non-infarcted area. In the infarcted region, the necrotic tissue is substituted by fibrous scar tissue. At the later phases of the healing process, the contraction of the fibrotic area occurs[8]. On the other hand, in the non-infarcted area of the left ventricle, different degrees of cardiac hypertrophy occur,

such as adaptation to the loss of the myocytes. Due to these alterations, the measurement of the infarction size by volume or area can result in error, as the resorption and retraction of the infarcted area, added to the hypertrophy of the non-infarcted region, can result in the underestimation of the infarction size in relation to the original infarcted area[12,14,20].

Another method used to determine the size of the infarction is the measurement of the internal perimeter of the infarcted segment, in relation to the total perimeter of the ventricular cavity. This analysis can be attained by two methods: echocardiogram and histology. However, similarly to the estimate made by area, these methods can present important limitations. Simultaneously to the necrosis of the myofibrils, there is interfibrillar collagen disintegration by the activation of proteolytic enzymes. This fact causes loss of the support tissue, which makes the region more distensible and, consequently, more susceptible to deformations. Thus, the slippage of muscular necrotic areas can occur, with the realignment of the myocytes on the infarcted wall. As a result, there is a narrowing of the region and dilation of the infarcted segment. This acute dilation, characterized by the thinning and distension of the infarcted region is called the infarction expansion[21-23]. Therefore, as a consequence of the expansion, the measurement of the infarction size by the internal perimeters can overestimate the size of the AMI[20].

Morphological characteristics

Regarding the anatomic characteristics of the rat's heart, the left coronary artery originates between the border of the left atrium and the pulmonary artery sulcus. Additionally, it was observed that the left coronary artery, in its proximal region, is usually intramyocardial, returning to the surface epicardially at approximately 3 to 4 mm from its origin[4]. The rat does not have a true circumflex artery[6]. The proximal region of the left coronary artery, practically at the ostium, gives origin to the septal branch and, farther down, to the branch that corresponds to the circumflex artery[17]. This anatomic characteristic ensures that the septal branch originates above the site where the coronary occlusion is performed. Thus, this model is characterized by presenting infarction of the left ventricular free wall, without involving the interventricular septum. Consequently, this region is used as control for morphological and biochemical studies[17].

Another anatomic characteristic of this model is that the rat has scarce collateral circulation, similarly to humans. The coronary occlusion invariably causes, therefore, transmural infarctions, making the subendocardial infarction a rare event, of around 3%[24].

Another pertinent aspect of this model is related to the involvement of the papillary muscle. Contrary to the dog model, in which the coronary occlusion leads to necrosis of the papillary muscle in 85% of the cases, the infarction model in rats is characterized by the preservation of posterior papillary muscle. The histological analysis showed that, in rats, the coronary occlusion does not affect or minimally affects this muscle. The explanation for this phenomenon is that the irrigation of the posterior papillary muscle is carried out by the septal branch of the left coronary artery, which, as discussed above, is not affected by the coronary occlusion[17].

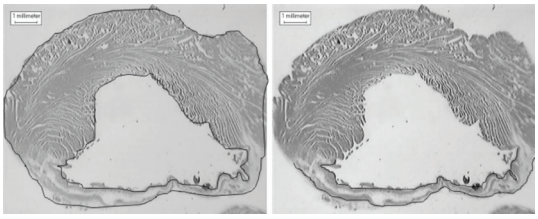

Figure 2 - Evaluation of the infarction size through the measurement of the epicardial and endocardial circumferences of the infarcted segments (right) in relation to the total epicardial and endocardial circumferences of the left ventricle (left).

Regarding the healing characteristics after the coronary occlusion, the rat model also shows some peculiarities[25-31]. The activation of metalloproteases (MMP), proteolytic enzymes responsible for collagen degradation, was identified 1 hour after the coronary occlusion[28]. Initially, the MMP degrades the fibrillar collagen and, subsequently, the MMP-2, MMP-3 and MMP-9 degrade these fragments[26]. A previous study suggests that, 3 hours after the coronary occlusion, around 50% of the collagen has been degraded[28]. This proteolytic activity ceases one week after the infarction[27]. Concomitant to the proteolytic activity, other alterations have been identified. After 24 hours, the muscular necrosis becomes evident, initially followed by a neutrophilic infiltration and later, by a lymphocytic and monocytic infiltrate[30]. Three to four days after the coronary occlusion, the accumulation of fibroblast-like cells start, but with actin in its composition, the myofibroblasts.

It is accepted that the myofibroblasts are fibroblasts modified by the TGF-β secreted by the monocytes and responsible for the synthesis of collagen I and III, which starts to accumulate in the peripheral region of the infarction on the third day and becomes well organized 14 days after the AMI. The healing process is complete 21 days after the coronary occlusion[25-31].

Another aspect that must be considered is that, in animals with large infarctions, the non-infarcted areas of the left ventricle and the of the right ventricle show an increase in the expression of pre-collagen types I and III mRNA, starting between 4 to 7 days after the AMI, which can result in the accumulation of progressive collagen. Therefore, large infarctions are often accompanied by different degrees of fibrosis in the non-infarcted areas[26].

One of the main characteristic of myocardial infarction is associated to the fact that the loss of contractile tissue triggers an adaptive cell growth process in the non-infarcted tissue[32-37]. In the rat model, the left ventricular hypertrophy is characterized for having an eccentric pattern, being an early event and being detectable on the third day after the coronary occlusion.

After three to four weeks, the degree of hypertrophy increases between 30% and 60%. Hypertrophy can also occur in the right ventricle, characteristically with a concentric pattern and correlated to increases in the left-ventricular end-diastolic pressure and right ventricular

systolic pressure[12]. However, similarly to what occurs in the infarcted ventricle, the right ventricular hypertrophy is present on the third day and affects around 30% at the end of one month[38,39].

Finally, similarly to what occurs in the infarcted area, the non-infarcted area, mainly the one that separates the infarcted tissue from the non-affected tissue, can also be the target of MMP activation. As a consequence, bundles of viable myocytes can undergo muscular slippage and realignment processes (side-to-side slippage)[40].

Thus, as a consequence of the processes of expansion, of ventricular hypertrophy (of eccentric characteristic) and of cell slippage in the region that is borderline with the infarction area, the infarcted cavity can increase in diameter and lose its normal elliptical geometry, taking on a spherical configuration. These changes in size, mass and ventricular geometry clinically characterize the process of cardiac remodeling after the infarction[41-47].

Functional characteristics

The hemodynamic consequences caused by the coronary occlusion in the rat have been well documented. Different studies have shown that the infarction causes the decrease of several functional variables, such as systolic volume, cardiac output, left ventricular systolic pressure, first positive pressure derivative and negative pressure derivative. In parallel, there is an increase in the left ventricular-end diastolic pressure and of the decline time constant of the isovolumetric pressure. The infarction is accompanied, therefore, by systolic as well as diastolic dysfunctions, which are identified as early as 3 hours after the coronary occlusion[12,48-51].

Regarding the mechanisms involved in the ventricular dysfunction, there is evidence that up to the three first weeks after large infarctions, the non-infarcted muscle function is normal, although the chamber function is depressed[37]. On the other hand, after 6 weeks, the muscular function is depressed[52]. Thus, this evidence suggests that, initially, the ventricular dysfunction is a consequence of the loss of contractile tissue, secondary to the infarction. Chronically, however, the remaining muscle becomes dysfunctional, probably due to the post-infarction remodeling process.

One of the main characteristics of this model is that the functional alterations are closely related to the size of the infarction. Therefore, rats with infarctions < 30% did not present hemodynamic abnormalities. Animals with moderate infarctions (31-46%) had normal basal hemodynamic values, but reduced pressure-generating capacity. On the other hand, rats with large infarctions (> 46%) presented heart failure, with elevated filling pressures and cardiac output decrease[12]. Therefore, this model allows the study of different degrees of ventricular dysfunction.

Finally, the experimental infarction model in rats allows the evaluation of the right ventricular function. Thus, in a previous study, in which an isolated heart preparation was used, perfused with a nutrient solution, a decrease in the systolic pressure was identified, which correlated, in linear form, with the increase in the right ventricular mass[53].

Morphological, functional and clinical evaluation of heart failure

To evaluate hypertrophy in different models of cardiac injury, the ratio between the left ventricular weight, adjusted by the body weight of the animal of by the tibia, is commonly used.

In the infarction model, however, the complex interaction of events such as the resorption of the necrotic tissue and the amount of collagen of the scar can interfere with the weight of the infarcted ventricle so that it won't reflect the actual cell growth. Therefore, the use of the myocyte transversal diameter is preferable for the evaluation of the degree of left ventricular hypertrophy in this model[54]. On the other hand, to determine the right ventricular hypertrophy, ratios with body weight can be used[55].

To evaluate the amount of collagen of the non-infarcted tissue, the most commonly used methods are: hydroxyproline measurement[56], interstitial collagen fraction[57] and detection of collagens I and III[26] through the RNA analysis or anti-collagen I and III antibodies. An important fact is that, although it is an indirect method, a close correlation between the biochemical method and the amount of collagen analyzed by morphometry was verified[58,59].

For the functional assessment, several methods are available: analysis by the papillary muscle[60], isolated heart[61,62] and invasive hemodynamic evaluation[12,63]. In the recent years, however, the echocardiogram has become increasingly important in the morphological and functional assessment of infarcted rats. There are several functional variables that can be used, but the most frequent ones are: variation in area fraction, shortening fraction, cardiac output, segmental wall motion score, transmitral flow and cardiac performance index[51,64-67].

There are several clinical variables that can be used for the diagnosis of heart failure in this model, among which are: general appearance, slow movements, alterations in fur texture, delayed growth, body weight and dyspnea. These variables, however, can be little sensitive for the diagnosis of congestion or low cardiac output[12]. The first studies for the clinical detection of heart failure signs in rats were carried out by Bing and cols. that studied spontaneously hypertensive rats with heart dysfunction[68-70]. The data on the incidence of post-infarction heart failure and the possibility of its clinical recognition in rats, however, are scarce. Recently, using the rat model with moderate and large infarctions, the observed prevalence of clinical and anatomopathological signs of heart failure was tachypnea, (46%); liver congestion, (21%); thrombus in the left atrium, (21%); ascites, (25%); pleural-pericardial effusion, (71%) and right ventricular hypertrophy, (100%)[71].

Implications

The first implication of this model is related to the fact that, as it frequently results in large transmural infarctions located in the anterior wall, the infarction model in rats is ideal for the study of the physiopathology of post-infarction remodeling,

as these variables are the great determinants of the presence and intensity of the remodeling process[41-47].

Another implication is the similarity with the physiopathological alterations that occur after infarctions in humans[52]. For this reason, this model is ideal for the study of therapeutic interventions to minimize the morphological and functional alterations that can occur after the infarction. Thus, many of the interventions used in infarction patients were initially analyzed in the rat model, such as: angiotensin-converting enzyme inhibitors[14,41], angiotensin-II receptor antagonists[72], aldosterone antagonists[73] and betablockers[74].

As demonstrated, the experimental infarction model in rats has been widely used for the study of the outcomes that occur after the coronary occlusion. Due to the animal's inherent characteristics, we believe that the discussion of the main aspects of this model is extremely useful for those dedicated to the study of the acute myocardial infarction.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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