

Research Technical Note

Translational Physiology of Myocardial Infarct (MI): Considerations of Rodent Cardiovascular Physiology in Mimicking the Human Condition

The main aspect of post-myocardial infarct/infarction (MI) research is to mimic conditions that lead to the development of myocardial ischemia. MI indicates irreversible myocardial injury resulting in necrosis of a significant portion of myocardium. Human clinical MI may be either of the non-reperfusion type, if the obstruction to blood flow is permanent, or the reperfusion type, if the obstruction is reversed after myocardial cell death. The infarct-affected areas are limited by distribution of the occluded vessel(s). In humans, the left main coronary artery occlusion generally results in a large antero-lateral and septum infarct, whereas occlusion of the left anterior descending coronary artery causes necrosis limited to the anterior wall. Hospital post-mortem findings in most cases reveal an acute thrombus overlying an atherosclerotic plaque in the coronary arteries. In these examples of vascular distribution, recreating this instance in animal research models has proved challenging due to the limitations caused by the fundamental difference between human and rodent cardiovascular physiology, carotid artery disease (CAD), and cellular and genetic makeup. Additionally, in the human population there is a known genetic polymorphism involving pathways of lipids, coagulation, and the renin-angiotensin system which does not currently have a known rodent analog.

CREATION OF RODENT MI MODEL

The natural development of MI stems from atherosclerosis (athero-gruel/sclerosis-hardening) plaque growth which occludes blood flow or suddenly ruptures. There is, however, difficulty in re-creating plaque growth in animal models which consistently leads to MI. Several diet supplementation methods have been used to simulate this natural disease progression. First, feeding cholesterol-rich diet can lead to chronic narrowing of coronary arteries and hypercholesterolemia, making them vulnerable to plaque buildup and thrombosis (1). Additionally, using mice lacking apoE^{-/-} and LDLr^{-/-} in combination with a high fat diet accelerates disease progression (2). While very similar to the natural mechanism, these methods are difficult to replicate due to the inherent variability of plaque behavior. One of the complexities to studying vulnerable plaques is that they do not produce a significant stenosis before they rupture and cause an acute MI. Additionally, some of the vulnerable plaques are short-lived and might resolve spontaneously. This plaque behavior makes its development hard to detect or track. Finally, it can be very complex to control the location or extent of MI when it occurs. Due to these difficulties with animal model disease-like-state recreation, interventional (surgery) models are often used.

There are two main interventional methods of MI induction in rodents, vascular occlusion and cryoinjury. Vascular occlusion can be used to either fully, partially or temporary restrict blood flow through a coronary artery. In rodents there are temporary occluders such as hanging weights (3), and different methods of permanent or temporary suture ligation (1, 4). There are also other methods for occlusion of coronary arteries mostly in large animals including: occluders (U-shaped, ring-shaped, ameroid constrictors), balloon inflation in coronary artery.

Translational Physiology of Myocardial Infarct Cont.

CREATION OF RODENT MI MODEL CONT.

Currently the preferred method of introduction of MI in rodents is permanent suture ligation of the left descending coronary artery. The advantage of using permanent occlusion is that it mimics the behavior of a complete plaque blockage by inducing hypoxia and ischemia. It is important to note that rodent coronary arteries have different locations and branching patterns as compared to human coronary arteries (5, 6, and 7). For example, rats do not have the circumflex artery (8), therefore, the proximal region of the left coronary artery gives origin to the septal branch and to the branch that corresponds to the circumflex artery (9).

An alternative method to occlusion is creation of infarction by freeze-thaw injury (10) or cryoinjury (11, 12). This method allows for a specific region of tissue to be damaged unconstrained of coronary artery physiology. While this method has good reproducibility, it is less physiologically relevant as it causes tissue injury by different mechanism(s). This in turn impacts the response to infarct as seen by the delayed remodeling as compared to occlusion induced infarcts (12). Since a capable trained rodent surgeon is able to create permanent suture ligations with high reproducibility, using freeze-thaw or cryoinjury methods as MI induction model requires careful consideration for its translation and should be subjected to careful scrutiny before the project begins.

A common downside to artificially induced rodent myocardial infarcts is its relative low-emergence of other clinical symptoms associated with heart failure (pulmonary congestion, chest tightness, dyspnea, cachexia, ST-elevation myocardial infarction (STEMI) and non ST-elevation infarction (non-STEMI)). Additionally, there are a lack of rodent observational studies that pay specific attention to morbidity and mortality post-MI resulting from arrhythmias, cardiac rupture, heart failure, valve insufficiency, and embolization. As these comorbidities have the potential to alter the type, timing or extent of physiological responses, many rodent models are inherently limited in their clinical pathophysiology-translational bench-to bedside value.

CELLULAR AND GENETIC INFLUENCES

The heart's response to stresses such as MI is influenced, in part, by cellular phenotypic composition and genetics. For example, an adult mouse heart consists of approximately 45% non-cardiomyocytes and 55% cardiomyocytes, whereas adult rat and human hearts consists of around 70% of non-cardiomyocytes and 30% of cardiomyocytes (13). More studies are necessary to better characterize the two major cell types and their roles, including their intercellular interactions, during and post-MI. Without this knowledge it is very challenging to determine if and, to what extent heart, cellular composition affects cardiac behavior.

Genetic variations within species also factor into cardiovascular behavior as seen by strain-dependent difference in mortality rates. In a study by Liu *et. al.* the mortality of Sprague-Dawley rats was 36%, whereas in Lewis inbred rats it was significantly lower at 16% (14). Mice mortality associated with MI induction ranges from 37–50% (15). Furthermore, when different genetic backgrounds of mice were studied post-MI the highest incidence of post-MI infarct rupture, which typically occurred at 3–6 days post-MI, was in 129S6 mice (62%), followed by C57Bl6 (36%), FVB (29%), Swiss (23%), and BalbC (5%) (16). This incidence of high infarct rupture in 129S6 strain mice was associated with highest systolic blood pressure and presence of inflammation in the area. It must then be determined if those responses (high BP and inflammation) are physiologically accurate. Once the importance and relevance of genetically controlled comorbidities are determined, they aid in choosing an appropriate translational model.

Translational Physiology of Myocardial Infarct Cont.

DISEASE RESPONSE BEHAVIOR

Equally important in mimicking a post-MI condition is having a meaningful biological response. In case of arrhythmias originating from post myocardial injury, there are differences between rodents and humans due to the dissimilar locations of major cardiac electrical axis. Different apoptosis progression, heart rate, and activity of various ionic channels also play a role in arrhythmias (17). However, the rat animal model can be ideal as compared to human in the assessment of various therapeutic interventions addressing arrhythmias due to a high frequency of ischemic ventricular arrhythmias in a repetitive, self-terminating manner (18).

Myocardial infarct size and LV chamber dilation are more pronounced in experimental rodent model systems as compared to human infarct. This adds an additional level of complexity to comparing infarct severity between species. According to the Killip-Kimball classification of infarct size on LV dysfunction, Class I is for small infarcts while Class IV is the most severe (the majority being fatal) with major necrosis involving more than 30% of the LV free wall. Similar pre-clinical classification of infarct size or method of correlating rodent infarct to the Killip-Kimball system is missing in animal models. This important classification can be incorporated into rodent models given the fact that rodent infarcts usually involve a much larger percentage of the cardiac tissue. At 21 days post-MI, rats with small MI (i.e. 4-30%) have no apparent impairment in baseline hemodynamics or peak indices of pumping and pressure generating ability when compared to the sham non-MI rats. Moderate MI between (31- 46%) is associated with normal baseline hemodynamics, but reduced peak flow indices and developed pressure. Large MI (46% and more) present congestive heart failure, with elevated filling pressures, reduced CO, and a minimal capacity to respond to pre- and afterload stresses (19). Note: In rodents the same percentage of infarct size (30%) which corresponds to severe in humans is classified as small, with minimal long term effects.

Remodeling behavior in rodents has some distinct differences as compared to humans. Post-MI cardiac remodelling in rodents is characterized by biventricular remodelling such that myocytes from the LV, RV and intra-ventricular septum are elongated to about the same extent, and thickness of septum increases (20). In humans, remodeling is centralized to the damaged ventricle.

CONCLUSION

The complex and multifaceted process of post myocardial infarct behavior precludes the study of a single animal model as being fully representative of the changes occurring in patients. Information combined from both large and small animal myocardial infarct models might help unravel key pathophysiological, cellular and gene mechanisms and provide the foundation for testing potential therapeutic strategies. Careful consideration of an experimental protocol increases its translational value.

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Translational Physiology of Myocardial Infarct Cont.

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