jove

Innovative Animal Models Of Cardiac Remodeling: Development And Evaluation

Feng Hua Yang[1], **W. Glen Pyle**[2,3], **Yihua Bei**[4]

[1] Cardiovascular Model Research Center, Guangdong Laboratory Animals Monitoring Institute [2] IMPART Investigator Team, Dalhousie Medicine [3] Department of Biomedical Sciences, University of Guelph [4] School of Medicine, Shanghai University

Corresponding Author

Feng Hua Yang
fenghua.yang@gdlami.com

Citation

Yang, F.H.,Pyle, W.G.,Bei, Y. Innovative Animal Models Of Cardiac Remodeling: Development And Evaluation. *J. Vis. Exp.* (193), e65019, doi:10.3791/65019 (2023).

Date Published

March 3, 2023

DOI

10.3791/65019

URL

jove.com/video/65019

Editorial

The term cardiac remodeling has been used to describe changes in the structure or function of the heart caused by various stressors since the term was first coined by Hochman and Bulkley in the myocardial infarction (MI) model in the early 1980s[1,2]. Remodeled hearts may exhibit systolic or diastolic dysfunction, arrhythmias, ventricular wall hypertrophy, scarring, vascular abnormalities, fibrosis, myocyte death, inflammation, metabolic disturbances, and cellular and molecular changes[3]. The consequence of this cardiac remodeling is often heart failure. Animal models are essential tools for identifying the mechanisms of disease and exploring intervention strategies to attenuate and reverse cardiac remodeling. The objective of this methods collection is to introduce innovative approaches for developing mouse or minipig models of cardiac remodeling. The inclusion of different animals allows for the movement of research from the basic, exploratory investigations that use rodents, to the pre-clinical model of pigs. The strategies used by the authors include right ventricular MI induced by right coronary artery ligation in mice[4], programmed electrical stimulation-induced cardiac arrhythmias in mice[5], vein graft disease induced by coronary artery bypass grafting (CABG) in pigs[6], cardiac volume overload due to aortic regurgitation in mice[7], heart failure with preserved ejection fraction (HFpEF) induced by descending aortic constriction in pigs[8], combined angiotensin II infusion and renal denervation to control blood pressure in mice[9], and mutations in a human homologous gene, cardiac myosin heavy chain 7 gene (*MYH7*), in mouse hearts[10]. In addition, the authors provide detailed protocols for assessing cardiac remodeling using cardiac magnetic resonance feature tracking (CMR-FT) in patients[11], echocardiography in mice and pigs[4,7,8,10], electrophysiological recordings in mice[5], hemodynamics measurements in mice[4,7], mouse or pig heart histology[4,6,7,8,9,10], and biomarkers[6,8,9].

Myocardial infarction is the most common cause of cardiac remodeling[12]. Right ventricular involvement is known to be associated with an increased risk of death from inferior MI[13,14]. The left coronary artery ligation model has been widely used to simulate the clinical features of MI[15,16]. Therefore, Liao et al.[4] develop a mouse model focusing on right ventricular MI using permanent ligation of the right coronary artery. The authors demonstrate the mouse cardiac surgery procedures and methods to determine the

right ventricular function, hemodynamics, and histology. In addition, representative images of coronary vascular casts in mice are provided. The introduction of a right ventricular MI model will facilitate the understanding of the mechanisms that trigger cardiac remodeling after myocardial infarction in the more rarely investigated right heart.

CABG is used to treat prolonged MI or multivessel coronary artery diseases. However, vein grafts can undergo pathological changes and re-occlude after surgery, leading to vein graft disease[17]. Li et al.[6] detail a porcine CABG procedure using the internal mammary vein as a graft[6]. In addition, the authors demonstrate the method of pig tracheal intubation and the harvesting procedure of the left internal mammary vein. This model can be used to test treatments that maintain the patency of vein grafts or reduce adverse graft remodeling.

Atrial and ventricular arrhythmias are frequently diagnosed in patients with acute MI[18,19]. Although mouse models have limitations in terms of studying cardiac arrhythmias due to their high heart rate and small body size, researchers have managed to record and manipulate mouse electrocardiograms to gain valuable insight into the electrical changes of the heart post-MI. In this context, Lu et al.[5] combine programmed electrical stimulation and isolated heart perfusion to study ventricular tachyarrhythmias in MI mice. The authors also demonstrate the use of an echocardiography-guided injection of recombinant virus in mouse and rat ventricles. The techniques described in this article are valuable for studying the cardiac rhythm disturbances associated with adverse cardiac remodeling after MI.

Atrial arrhythmias are independent risk factors for atrial remodeling and dysfunction. Wang et al.[11] apply CMR-FT to assess left atrial strain and atrial function in patients, enabling the accurate assessment of atrial dysfunction. With advances in clinical MRI diagnostic techniques, researchers have employed this approach to assess cardiac structural and functional abnormalities in mouse and porcine models[20,21]. The method presented by Wang et al.[11] can also be employed to assess atrial function in large animal models.

Cardiac volume overload can be caused by aortic regurgitation, a condition in which diastolic blood leaks from the aorta into the left ventricle[22]. Based on the Framingham Heart Study, the prevalence of aortic regurgitation in men and women is 13% and 8.5%, respectively[23]. Wu et al.[7] present a mouse model of aortic regurgitation that mimics the cardiac volume overload caused by valvular heart disease. In this protocol, aortic valve rupture surgery is performed under the guidance of high-resolution ultrasound. The cardiac function, hemodynamic consequences, and puncture sites on the valves of the model are presented.

About half of heart failure patients are classified as HFpEF[24]. Li et al.[8] establish a minipig model of HFpEF induced by the precise constriction of the descending aorta. The authors demonstrate the open-heart surgery, the setup of the aortic pressure measurement device, the measurements using transthoracic echocardiography, and the ventricular remodeling process.

Wang et al.[9] demonstrate a renal sympathetic denervation protocol to control hypertension and attenuate cardiac hypertrophy in mice. In this mouse model, the authors first implant an osmotic micropump containing angiotensin II and then use a delicate approach to desensitize the nerve endings in the renal artery wall. Additionally, anatomical images of the mouse renal arteries are presented. This well-designed

model aids in studying the mechanisms of cardiac remodeling induced by hypertension.

Hypertrophic cardiomyopathy is the most common inherited heart disease[25], and sarcomere gene variation is a major cause of hypertrophic cardiomyopathy. In this context, Xia et al.[10] demonstrate comprehensive methods for understanding the genetic factors associated with this disease. The authors first identify MYH7 variants using exome sequence and variant segregation analyses and then create a mouse model with a point mutation in the MYH7 gene. The pathological phenotypes of cardiac hypertrophy are shown in the article.

The authors included in this methods collection have established different models of cardiac remodeling by improving existing procedures or employing new techniques. It is expected that these innovative modelscan be developed to uncover the molecular mechanisms of cardiac remodeling, advance our understanding of the human conditions, and create novel treatment and diagnostic strategies that improve patient outcomes and prolong lives.

Disclosures

The authors have nothing to disclose.

Acknowledgments

This work was supported by Guangdong Science and Technology Program 2008A08003 (F.H.Y.), 2022A1515012338 (F.H.Y.), 2022A1515011154 (F.H.Y.), Canadian Institutes of Health Research Grant MOP126077 (W.G.P), Heart and Stroke Foundation of Canada Grant G-21–0031543 (W.G.P.), Natural Sciences and Engineering Research Council of Canada Grant RGPIN-2018–04732 (W.G.P), and Guangdong Provincial Key Laboratory of Laboratory Animals (2017B030314171).

References

1. Hochman, J. S., Bulkley, B. H. Expansion of acute myocardial infarction: An experimental study. *Circulation.* **65** (7), 1446-1450 (1982).
2. Cohn, J. N., Ferrari, R., Sharpe, N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *Journal of the American College of Cardiology.* **35** (3), 569-582 (2000).
3. Burchfield, J. S., Xie, M., Hill, J. A. Pathological ventricular remodeling: mechanisms: Part 1 of 2. *Circulation.* **128** (4), 388-400 (2013).
4. Liao, R. et al. Generation and characterization of right ventricular myocardial infarction induced by permanent ligation of the right coronary artery in mice. *Journal of Visualized Experiments.* (180), e63508 (2022).
5. Lu, A. et al. Viral transgene expression in rodent hearts and the assessment of cardiac arrhythmia risk. *Journal of Visualized Experiments.* (185), e64073 (2022).
6. Li, X. et al. Establishment and evaluation of a porcine vein graft disease model. *Journal of Visualized Experiments.* (185), e63896 (2022).
7. Wu, J. et al. Surgically induced cardiac volume overload by aortic regurgitation in mouse. *Journal of Visualized Experiments.* (186), e63579 (2022).
8. Li, X. et al. A surgical model of heart failure with preserved ejection fraction in Tibetan minipigs. *J Vis Exp.* (180), e63526 (2022).

9. Wang, M. et al. Improved renal denervation mitigated hypertension induced by angiotensin II infusion. *Journal of Visualized Experiments.* (183), e63719 (2022).
10. Xia, Y. et al. Investigating the pathogenesis of MYH7 mutation Gly823Glu in familial hypertrophic cardiomyopathy using a mouse model. *Journal of Visualized Experiments.* (186), e63949 (2022).
11. Wang, Y., Gao, H., Li, Y., Sun, H., Liu, L. Estimating bilateral atrial function by cardiovascular magnetic resonance feature tracking in patients with paroxysmal atrial fibrillation. *Journal of Visualized Experiments.* (185), e63598 (2022).
12. Sutton, M. G., Sharpe, N. Left ventricular remodeling after myocardial infarction: Pathophysiology and therapy. *Circulation.* **101** (25), 2981-2988 (2000).
13. Mehta, S. R. et al. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. *Journal of the American College of Cardiology.* **37** (1), 37-43 (2001).
14. Sanz, J., Sánchez-Quintana, D., Bossone, E., Bogaard, H. J., Naeije, R. Anatomy, function, and dysfunction of the right ventricle: JACC state-of-the-art review. *Journal of the American College of Cardiology.* **73** (12), 1463-1482 (2019).
15. Lindsey, M. L. et al. Guidelines for in vivo mouse models of myocardial infarction. *American Journal of Physiology-Heart and Circulatory Physiology.* **321** (6), H1056-H1073 (2021).
16. Cops, J., Haesen, S., De Moor, B., Mullens, W., Hansen, D. Current animal models for the study of congestion in heart failure: An overview. *Heart Failure Reviews.* **24** (3), 387-397 (2019).
17. de Vries, M. R., Simons, K. H., Jukema, J. W., Braun, J., Quax, P. H. Vein graft failure: From pathophysiology to clinical outcomes. *Nature Reviews Cardiology.* **13** (8), 451-470 (2016).
18. Schmitt, J., Duray, G., Gersh, B. J., Hohnloser, S. H. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *European Heart Journal.* **30** (9), 1038-1045 (2009).
19. Bigger, J. T., Jr., Fleiss, J. L., Kleiger, R., Miller, J. P., Rolnitzky, L. M. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation.* **69** (2), 250-258 (1984).
20. Daal, M. R. R. et al. Quantification of mouse heart left ventricular function, myocardial strain, and hemodynamic forces by cardiovascular magnetic resonance imaging. *Journal of Visualized Experiments.* (171), e62595 (2021).
21. Brenner, G. B. et al. Post-myocardial infarction heart failure in closed-chest coronary occlusion/reperfusion model in Göttingen minipigs and Landrace pigs. *Journal of Visualized Experiments.* (170), e61901 (2021).
22. Bekeredjian, R., Grayburn, P. A. Valvular heart disease: Aortic regurgitation. *Circulation.* **112** (1), 125-134 (2005).
23. Singh, J. P. et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *American Journal of Cardiology.* **83** (6), 897-902 (1999).
24. Dunlay, S. M., Roger, V. L., Redfield, M. M. Epidemiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology.* **14** (10), 591-602 (2017).

25. Maron, B. J., Maron, M. S. Hypertrophic cardiomyopathy. *Lancet.* **381** (9862), 242-255 (2013).