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Commentary: Cause or consequence? The influence of mitral regurgitation on post-myocardial infarction structural remodeling is better defined using a new rodent model

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We remain perplexed if mitral regurgitation (MR) plays an important primary causative role in the poor clinical outcomes observed with maladaptive post-myocardial infarction (MI) structural remodeling. It is possible that MR is simply a consequence of structural chamber remodeling with minimal clinical significance when directly targeted by surgical therapy. Accordingly, understanding the complex mechanistic pathways that underlie this process is important for our targeted surgical therapies to have an impact.

Large preclinical animal models can provide a useful evaluation of the direct contribution of MR to structural cardiac remodeling.¹ However, large animals are cumbersome for more complex lesion sets and lack the molecular and genetic tools to perform mechanistic analysis in greater depth. In the September 2020 issue, Onohara and colleagues² present the development of a combined MR and MI model in rats. The rodent MI model is well validated to reflect human post-MI remodeling leading to heart failure³ and provides many pragmatic advantages. It is inexpensive and offers high-throughput studies as compared with large animals. It is also highly clinically relevant. Therapeutic interventions that attenuate post-MI structural cardiac remodeling in this model have been translated into standard-of-care medical therapies⁴ that today we use routinely

Extensive post-MI remodeling as observed in a rodent infarct model of human disease.

CENTRAL MESSAGE

Adding a valve lesion to an established rodent model of ischemic injury provides a promising new platform to uncouple the contribution of mitral regurgitation to post-MI structural chamber remodeling.

(angiotensin-converting enzyme inhibitors, aldosterone antagonists, and beta-blockers).

By integrating this rodent MI model with their recently described MR model,⁵ the investigators tracked the functional consequences of an MR or MI lesion alone or in combination over time. Their findings corroborated large animal model work with MR significantly impacting left ventricular (LV) dilation and systolic function.¹ The temporal assessment represents a unique advantage of the model, as it provides critical insight into the kinetics of LV remodeling and could identify potential therapeutic windows for intervention. Changes in cardiac fibrosis associated with distinct expression profiles for extracellular matrix-related genes as assessed by gene array analysis were also noted between groups and highlight one facet of the diverse molecular toolbox that is uniquely available in rodent models. This model has defined functional readouts that allow more in-depth molecular evaluation of the key players involved in the remodeling process. For example, cells of the immune system, including those found within the pericardial space,⁶ have been associated with regulating LV remodeling and cardiac fibrosis following ischemic injury. It remains unclear how a valve lesion influences these inflammatory processes and regulates the observed changes in fibrosis.

From a therapeutic perspective, the benefits of surgical correction of MR in the postischemic setting are conflicting.

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Some studies have shown that surgical correction can positively impact patient outcomes,⁷ whereas others have not.⁸ Despite the promising data from the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial with MitraClip delivery,⁹ the mechanistic role of MR on post-MI remodeling should be defined. Our most effective therapies are best directed toward the underlying causes of disease and not their consequences. This new model provides an ideal platform for future investigators to characterize the structural remodeling process in more depth and represents an ideal starting point for the discovery of new therapies aimed at targeting the underlying cause of post-MI structural remodeling.

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