See Article page e333.

Commentary: Just shy of a bullseye!

Les James, MD, MPH, and Eugene A. Grossi, MD

In this paper, Kono and colleagues¹ created a tour de force rat model of ischemic cardiomyopathy with independently surgically induced mitral regurgitation (MR) to study the early and late effects of MR on left ventricle (LV) remodeling. Myocardial infarction (MI) was created by left coronary artery ligation, then either early or late severe MR was introduced at 4 or 10 weeks, respectively. Rats with MI only were used as controls. At 20 weeks from the index procedure, both end-diastolic volume and end-systolic volume were significantly larger in the groups with MR. In the MI-only group, maximal LV remodeling was observed until 6 weeks, after which point it plateaued. Conversely, in those with surgically induced MR, LV remodeling was increased and persisted for the duration of the study. From these results, the authors draw the conclusion that postinfarction MR, regardless of the timing of its onset, leads to adverse LV remodeling.

We congratulate the authors on a well-posed question and an elegant study design. The model, while exceptionally executed, was underused in that it did not sufficiently explore the regional histopathology in the injured, normal, and borderline areas of the myocardium.

A 2011 study from Soleimani and colleagues² from the University of California at San Francisco demonstrated that MR accelerates LV remodeling after MI, although it was unclear to what extent MR contributed to fiber and cross-fiber stress in the border zone and remote

CENTRAL MESSAGE

An exceptionally well-designed model studying effects of MR on LV remodeling may be further used to understand the pathophysiologic processes at work in remote areas of the myocardium.

myocardium of the LV.

Decreased

contractility in

the nonischemic border zone surrounding a MI is due in part to degradation of cardiomyocyte sarcomere components by intracellular matrix metalloproteinase-2. In addition, Schwarz and colleagues³ had shown previously that apoptotic markers are activated in the surviving myocardium remote from the infarct area as early as 1 day after MI and persist for up to 4 weeks. Work by Spaulding and colleagues⁴ published in 2018 showed that treatment with doxycycline in the post-MI period had the immediate and sustained effect of normalizing matrix metalloproteinase-2 levels, leading to increased wall thickness at end-systole and improved contractility in the border zone.⁴

In this study by Kono and colleagues,¹ the authors focused their investigative efforts on the effect of early and late MR on LV remodeling. While this is important, there was a missed opportunity to measure biomarkers in remote and border zones, which would have yielded an improved understanding of the pathophysiologic processes occurring in these regions.

The authors have given us an excellent model with compelling results. Might preserved tissue hold these answers? Additional investigation into processes at the cellular level in remote and border zones might elucidate possibilities for future interventional therapies and that would hit the bullseye.

From the Department of Cardiothoracic Surgery, NYU Grossman School of Medicine, New York, NY.

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Address for reprints: Eugene A. Grossi, MD, Department of Cardiothoracic Surgery, NYU Grossman School of Medicine, 530 First Ave, Suite 9V, Skirball Building, New York, NY 10016 (E-mail: Eugene.Grossi@nyulangone.org).

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See Article page e333.

Commentary: To screen or not to screen? That is the question—

Stephen H. McKellar, MD, MSc

Of all the memorable lines in William Shakespeare's *Hamlet*, perhaps the most famous one, is "To be, or not to be? That is the question."² For purposes of commenting on this article, perhaps it can be modified to "To screen, or not to screen? That is the question" and applied to this innovative preclinical study of myocardial infarction (MI) and mitral regurgitation (MR) by Kono and colleagues³ in this issue of the *Journal*.

In their elegant animal study, the authors attempt to answer the question whether early or late MR has a greater impact on left ventricular remodeling following MI. They induced MI in rats with coronary artery ligation and then randomized them to 1 of 3 groups: MI alone, MI + early MR, or MI + late MR. The authors observed significantly worse left ventricular remodeling in the 2 MI + MR groups compared with the MI-alone group, with no differences between the early and late MR groups. The authors conclude that MR has a strong impact on remodeling, regardless of whether it appears early or late, following MI.

This observation has important clinical implications with respect to screening for MR following MI, as it appears any

Hamlet's Vision by Pedro Amerigo.¹

CENTRAL MESSAGE

Mitral regurgitation adversely impacts left ventricular remodeling regardless of whether it appears early or late following myocardial infarction.

MR, early- or late-onset, is clinically relevant. This then begs a host of questions as to how often patients should be screened with echocardiography for the development of MR following MI. Once found, which severities of MR require intervention? Should standard quantitative indications for MR be applied in the patient after MI, or is there a role for earlier intervention, given the risk of adverse remodeling? Finally, should surgical or transcatheter repair should be used for patients who develop MR even if there isn't concomitant pathology be corrected if early intervention is warranted?

The relationship between MR and MI has long been and continues to be an area rife with unanswered questions. Clearly, there is much we don't know about the interaction between ischemic heart disease, MR, and reverse ventricular remodeling. This preclinical study adds insights into the temporal relationships between these entities and pushes the field toward additional questions to be studied and answered.

From the Division of Cardiovascular and Thoracic Surgery, Intermountain Medical Center, Murray, Utah.

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Address for reprints: Stephen H. McKellar, MD, MSc, Division of Cardiovascular and Thoracic Surgery, Intermountain Medical Center, Eccles Outpatient Center, 5169 Cottonwood St, Suite 600, Murray, UT 84107 (E-mail: stephen.mckellar@imail.org).

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