Moderate Ischemic Mitral Regurgitation After Posterolateral Myocardial Infarction in Sheep Alters Left Ventricular Shear but Not Normal Strain in the Infarct and Infarct Borderzone

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Background. **Chronic ischemic mitral regurgitation (CIMR) is associated with poor outcome. Left ventricular (LV) strain after posterolateral myocardial infarction (MI) may drive LV remodeling. Although moderate CIMR has been previously shown to affect LV remodeling, the effect of CIMR on LV strain after posterolateral MI remains unknown. We tested the hypothesis that moderate CIMR alters LV strain after posterolateral MI.**

Methods. **Posterolateral MI was created in 10 sheep. Cardiac magnetic resonance imaging with tags was performed 2 weeks before and 2, 8, and 16 weeks after MI. The left and right ventricular volumes were measured, and regurgitant volume indexed to body surface area (regurgitant volume index) was calculated as the difference between left ventricle and right ventricle stroke volumes divided by body surface area. Three-dimensional strain was calculated.**

Results. **Circumferential strain (E_{cc}) and longitudinal strain (E_{ll}) were reduced in the infarct proper, MI borderzone, and remote myocardium 16 weeks after MI. In addition, radial circumferential (E_{rc}) and radial longitudinal (E_{rl}) shear strains were reduced in remote myocardium but increased in the infarct and borderzone 16 weeks after MI. Of all strain components, however, only E_{rc} was affected by regurgitant volume index ($p = 0.0005$). There was no statistically significant effect of regurgitant volume index on E_{cc}, E_{ll}, E_{rl}, or circumferential longitudinal shear strain (E_{cl}).**

Conclusions. **Moderate CIMR alters radial circumferential shear strain after posterolateral MI in sheep. Further studies are needed to determine the effect of shear strain on myocyte hypertrophy and the effect of mitral repair on myocardial strain.**

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Mitral regurgitation (MR) associated with posterolateral myocardial infarction (MI) affects 1.2 to 2.1 million patients in the United States, with more than 400,000 patients having moderate-to-severe MR [1]. In patients with mild left ventricular (LV) enlargement, moderate chronic ischemic mitral regurgitation (CIMR) increases the incidence of heart failure from 18% to 68% [2] and mortality from 39% to 62% [3]. CIMR is caused by leaflet restriction and annular enlargement. Leaflet restriction is due to remodeling of the posterolateral LV wall, which makes the posterior papillary muscle move relative to the mitral valve and thereby restricts mitral leaflet motion [4].

There is significant controversy about the added effect of CIMR on post-MI LV remodeling and the ability of mitral valve repair (MVR) to reverse LV remodeling after posterolateral MI. There are animal studies for [5–7] and against [8] an effect on post-MI remodeling and for [9] and against [10] an effect of MVR. Further, in patients, whereas the National Institutes of Health-supported Cardiothoracic Surgery Trials Network (CTS) Net study of MVR for moderate CIMR found no benefit [11], application of the Coapsys device in patients with moderate CIMR was associated with a survival advantage [12].

Knowledge of regional myocardial strain (deformation of a body with regard to its reference configuration), stress, and contractility will help us understand LV remodeling and the development of CIMR. First, it is likely that high strain and associated high stress in the myocardium may act as a triggers for post-MI LV remodeling [13]. Second, high-fidelity strain measurements are necessary to

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Abbreviations and Acronyms

BSA = body surface area
BZ = borderzone
CIMR = chronic ischemic mitral regurgitation
E_{cc} = circumferential strain
E_{cl} = circumferential longitudinal shear strain
E_{ll} = longitudinal strain
E_{rc} = radial circumferential shear strain
E_{rl} = radial longitudinal shear strain
ED = end diastole
ES = end systole
LV = left ventricular
MI = myocardial infarction
MR = mitral regurgitation
MRI = magnetic resonance imaging
MVR = mitral valve repair or replacement
OM = obtuse marginal coronary artery

construct computation models of the LV after posterolateral MI that are able to calculate the effect of CIMR on regional contractility [14].

The effect of CIMR on three-dimensional regional LV strain has not been previously measured. We used magnetic resonance imaging (MRI) with noninvasive cardiac tags [15] to calculate three-dimensional strain and to more accurately measure LV and regurgitant volumes. We tested the hypothesis that moderate CIMR alters LV strain after posterolateral MI in sheep.

Material and Methods

Animals used in this study were treated under a protocol approved by the San Francisco VA Medical Center's Institutional Animal Care and Use Committee and in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996.

Myocardial Infarction

Adult sheep underwent left thoracotomy and posterolateral MI, as previously described [16]. Briefly, when there were four obtuse marginal (OM) coronary branches, OM2 and OM3 were ligated [16]. However, it was fairly common for a sheep to have a large branched OM1, and in that case, the posterior branch of OM1 and OM2 were ligated.

Magnetic Resonance Imaging

Two weeks before MI and 2, 8, and 16 weeks after MI, echocardiography and cardiac MRI were performed, as previously described [17]. Cardiac MRI was performed using noninvasive tags, as previously described [15]. Isoflurane level and end-tidal CO_2 were monitored during the MRI. Isoflurane was maintained at 2% by infrared spectophotometry, and end-tidal CO_2 was kept between 25 and 30 mm Hg. In addition, if necessary, an infusion of neosynephrine was titrated to keep systemic blood pressure at 90 mm Hg.

Image Analysis

Contouring and surfacing of the left ventricle and right ventricle were performed, as previously described [18]. The borderzone (BZ) and MI interface was identified on cine MRI images. The BZ was defined as extending 1 cm from the infarct edge. Three-dimensional volumes of the left and right ventricles were calculated by piecewise integration of the space enclosed by the epicardial and endocardial surfaces throughout the cardiac cycle. End diastole (ED) and end systole (ES) were calculated as previously described [6].

The regurgitant volume was calculated as the difference between the left and right ventricular stroke volumes, and regurgitant fraction was calculated [6]. The LV volume at ED and ES and regurgitant volume were indexed to body surface area (BSA) [19].

The American Society of Echocardiography recommendations for MR severity were followed [20], with values indexed to take animal BSA into consideration. Specifically, low moderate MR in a human is defined by the American Society of Echocardiography as a regurgitant fraction between 30% and 39% and a regurgitant volume between 30 mL and 44 mL [20]. Assuming that the average adult human BSA equals 1.79 m^2 [21], the regurgitant volume index for low moderate MR in sheep would range from 16.8 to 24.5 mL/m^2.

Strain Calculation

The MRI tag postprocessing was performed as previously described [22]. Next, strain was calculated using a four-dimensional B-spline–based motion tracking technique [23]. All six nonlinear, Lagrangian (Green's) strain tensor components referred to cardiac coordinates (ie, circumferential, longitudinal, and radial) at 36 locations (12 sectors and 3 layers) in each short-axis plane/slice after corrections for through-plane motion were calculated (Fig 1). However, only strain from the middle layer is presented in the manuscript.

Postmortem Examination

Sheep were sacrificed 1 week after the 16-week MRI. The LV and MI areas (Fig 2) were determined and the percent MI area calculated [10].

Statistical Analysis

All values are expressed as mean ± SD. The significance level was set at p less than 0.05. A multivariate mixed effects analysis (Proc Mixed, SAS version 9.2; SAS Institute, Cary, NC) was performed. The following regression model was used:

$$\text{Strain} = \text{Time} + \text{Region} + \text{RegurgVolume}_i \tag{1}$$

where the dependent variable, *Strain,* is circumferential (E_{cc}), longitudinal (E_{ll}), or one of the three regional LV shear strains (radial circumferential [E_{rc}], radial