JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 70, NO. 23, 2017
ISSN 0735-1097
https://doi.org/10.1016/j.jacc.2017.10.013

Atrial Infarction and Ischemic Mitral Regurgitation Contribute to Post-MI Remodeling of the Left Atrium

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ABSTRACT

BACKGROUND Left atrial (LA) remodeling after an acute myocardial infarction (MI) is poorly characterized regarding its determinants or its effect on ischemic mitral regurgitation (MR) development.

OBJECTIVES The purpose of this study was: 1) to compare LA structural remodeling in experimental MI swine models recapitulating the effects of left ventricular (LV) dysfunction, ischemic MR, and left atrial infarction (LAI); and 2) to analyze how LA remodeling influences ischemic MR development.

METHODS Three models of MI were generated: 1) proximal left circumflex (LCx) coronary artery occlusion involving the LA branch (LAI group); 2) proximal LCx occlusion not involving the LA branch (LCx group); and 3) left anterior descending (LAD) occlusion (LAD group). Serial cardiac magnetic resonance scans were performed to define LA and LV remodeling and ischemic MR, and were correlated with histology.

RESULTS Occlusion of the LA branch (LAI group) induced a greater degree of LA dilation at 1 and 8 weeks post-MI than the LCx and LAD groups, along with early and severe impairment of LA function. In the LCx and LAD groups, LA dysfunction was less pronounced and not consistent. Development of ischemic MR was more pronounced in the LAI group than in the LCx group. Histology confirmed atrial infarction with extensive fibrosis in the LAI group and interstitial fibrosis in the LCx group. In the LAD group, LA remodeling was not observed by cardiac magnetic resonance or histology.

CONCLUSIONS We provide the first experimental evidence of the deleterious effect of acute LAI on atrial structural remodeling, characterized by early LA dilation, dysfunction, and fibrosis, and early occurrence of ischemic MR. (J Am Coll Cardiol 2017;70:2878–89) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Chronic heart failure (HF) is a major cause of death and hospitalization. Despite advances in patient care, incident HF in myocardial infarction (MI) survivors remains a major cost burden to health care systems (1). In the aftermath of acute MI, the classic predictor of future adverse events, including sudden cardiac death and HF development, is left ventricular ejection fraction (LVEF) (2). More recently, left atrial (LA) dilation has been proposed as a novel predictor of HF, providing independent prognostic value in addition to LVEF (3–5).

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In the early post-MI period, excessive LA dilation occurs in ~15% to 45% of patients (3–5). The main cause of LA dilation is thought to be increased atrial pressures due to LV dysfunction (6). However, little attention has been paid to 2 other potentially key contributors to post-MI LA remodeling: ischemic mitral regurgitation (MR) and atrial infarction. Ischemic MR is caused by LV remodeling and a geometric distortion of the mitral valve that alters normal leaflet coaptation (7). Previous studies have suggested a close association between ischemic MR and post-MI LA remodeling (8); however, it remains unclear whether LA remodeling is a cause or consequence. Atrial infarction remains a clinical challenge of unknown incidence and consequences, mainly due to the lack of reliable diagnostic markers (9). Recently, LA coronary branch occlusion has been identified as a complication in up to 15% of patients undergoing percutaneous coronary intervention, leading to a higher prevalence of atrial arrhythmias, periprocedural MI, and mortality (10), underscoring its clinical importance. The effect of left atrial infarction (LAI) on LA structure and function has not been explored before, and most of our current knowledge is derived from autopsy reports (11).

Atrial structural remodeling refers to the process of LA enlargement and mechanical function impairment that occurs in many cardiovascular conditions, including ischemic heart disease (12). From a clinical imaging perspective, atrial structural remodeling is defined as an increase in LA dimensions and impairment of the atrial phasic function components; from a histological perspective, the complex cellular changes in this remodeling process are poorly understood (12). Clinical and experimental observations suggest that interstitial fibrosis is a key phenomenon underlying atrial structural remodeling in conditions such as chronic HF and MR (13). Upon acute MI, the effects of overlapping factors such as pressure and volume overload, in addition to atrial ischemia, can lead to specific structural substrate remodeling that, to the best of our knowledge, has not been characterized.

The aim of this study was to provide new insight into the causes, mechanisms, and consequences of LA structural remodeling as a complication of acute MI. Three pig models of MI were created: 1) occlusion of the proximal left circumflex coronary artery (LCx) with concomitant occlusion of the LA branch (LAI group); 2) occlusion of the proximal LCx coronary artery without involvement of the LA branch (LCx group); and 3) occlusion of the left anterior descending artery (LAD) (LAD group).

The specific aims were: 1) to evaluate the incidence and progression of post-MI LA structural remodeling (in relation to the culprit coronary artery); and 2) to analyze the interplay of LA dilation (and scar formation) and post-MI LA function with LV remodeling (and scar formation) and the development of ischemic MR. These processes were assessed by noninvasive cardiac magnetic resonance (CMR) imaging at 1 and 8 weeks post-MI and histology after sacrifice at 8 weeks post-MI.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance
HF = heart failure
LA = left atrial
LAD = left anterior descending
LAI = left atrial infarction
LCx = left circumflex artery
LVEF = left ventricular ejection fraction
MI = myocardial infarction
MR = mitral regurgitation

METHODS

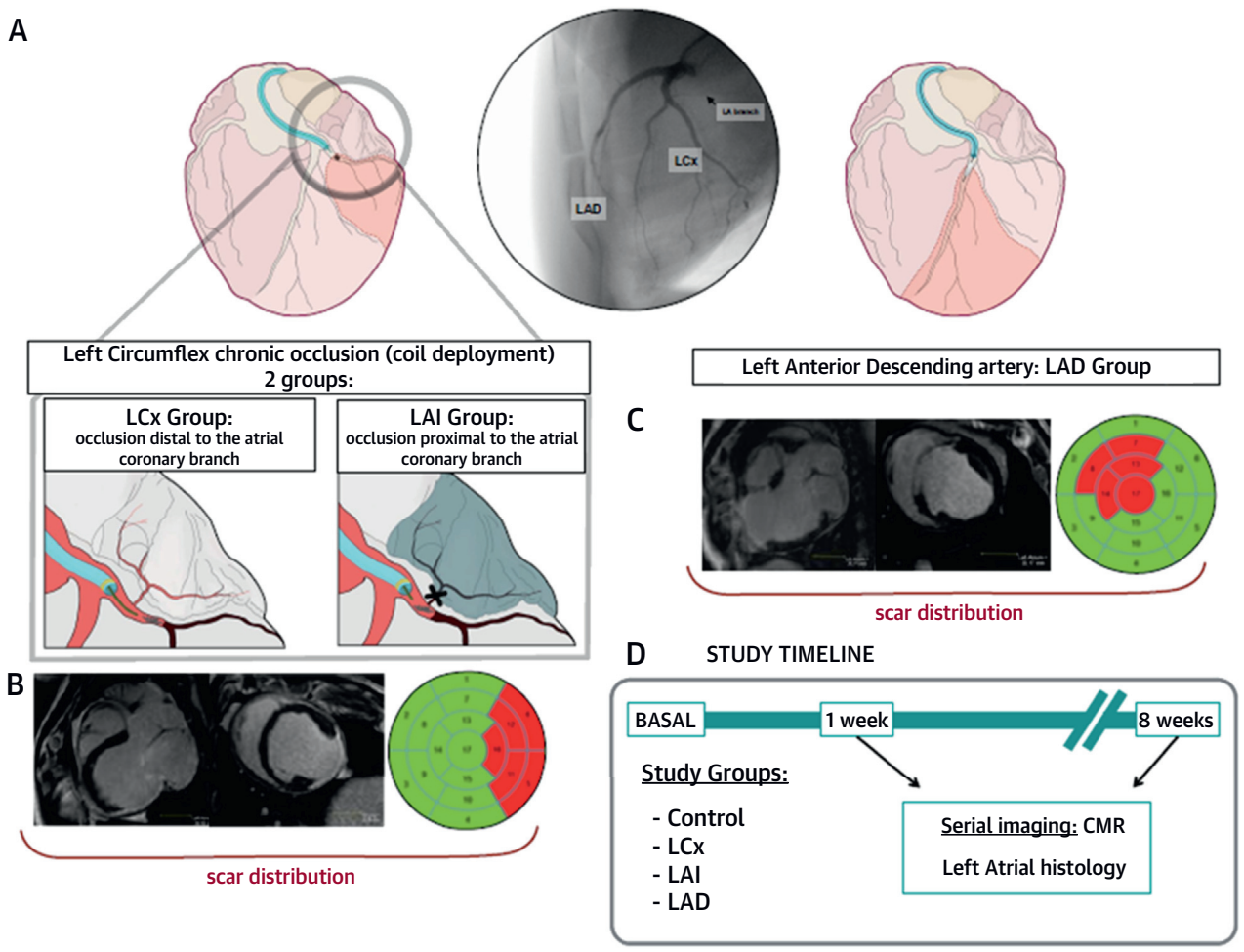
The study was approved by the institutional animal research committee and conducted in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals. An expanded description of experimental procedures is provided in the Online Appendix.

STUDY DESIGN. Closed-chest MI was induced in male large-white pigs (30 to 35 kg) by instrumentation of the LAD or LCx coronary arteries. LCx infarctions were divided into those with or without associated atrial coronary occlusion (see detailed description in the following text) and were used as model of ischemic MR. Anterior infarctions were generated by LAD ischemia-reperfusion to provide a post-MI model of LV dysfunction. Three experimental groups were created (**Figure 1**): 1) LCx occlusion (LCx group, n = 7

and CNIC. Dr. Sanchez-Gonzalez is an employee of Philips Healthcare. Dr. Delgado has received speaker fees from Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. William Stewart, MD, served as Guest Editor for this paper.

Manuscript received June 2, 2017; revised manuscript received September 28, 2017, accepted October 5, 2017.

FIGURE 1 Study Design and Experimental Procedures



(A) Two models of ischemic mitral regurgitation were created by left circumflex (LCx) chronic occlusion according to: 1) the absence of additional occlusion of the left atrial main branch (LCx group); or 2) its presence (left atrial infarction [LAI] group). A model of infarction with no ischemic mitral regurgitation was created by left anterior descending artery (LAD) ischemia (LAD group 3). **(B and C)** Typical scar segmental distributions. **(D)** The timeline of imaging and histology evaluation. CMR = cardiac magnetic resonance.

animals); 2) LCx occlusion involving the LA branch and therefore inducing LAI (LAI group, n = 8 animals); and 3) LAD occlusion to induce anterior MI (LAD group, n = 21 animals). A group of 4 healthy pigs was used as a control in the serial imaging studies. CMR imaging scans were obtained at baseline (before MI) and at 1 and 8 weeks post-MI to evaluate LA and LV structural remodeling and development of MR. Animals were sacrificed at 8 weeks post-MI and the hearts were excised for histological analysis of LA scarring and fibrosis.

MODELING CHRONIC POST-INFARCTION ISCHEMIC MR AND LAI. We established a technique for inducing ischemic MR in pigs that involves placing a coronary coil in the proximal segment of moderate-to-large LCx arteries (Online Appendix, Online Figure 1).

To evaluate the effect of acute LA injury during MI, animals undergoing LCx coiling were subclassified according to whether there was angiographic occlusion of the LA branch, which emerges from the proximal LCx segments or less frequently from the mid-LCx segment. Because the exact occlusion site was determined by the coil position after deployment at the proximal LCx artery, animals were assigned to the LCx or LAI groups upon examination of the final angiogram at the end of the catheterization procedure.

MODELING ANTERIOR ACUTE INFARCTION. To evaluate post-MI LA structural remodeling due to LV dilation

TABLE 1 Left Atrial Remodeling CMR Parameters: Time Course by Group

	Control (n = 4)		LCx (n = 7)		LAI (n = 8)		LAD (n = 21)	
	Baseline	8 Weeks	1 Week	8 Weeks	1 Week	8 Weeks	1 Week	8 Weeks
Maximal area, cm^2	13.1 (12.7–13.3)	18.8 (18.2–19.6)	19.5 (18.6–20.9)*†	25.8 (22–27)*†	22.6 (20.3–23.8)*†	32.6 (27.2–38.9)*†‡	13.8 (12.5–14.7)	15.6 (14.4–18.0)
Maximal indexed area, cm^2/m^2	15.7 (15.2–16.3)	15.3 (14.8–15.9)	19.9 (19.0–22.3)*†	17.0 (16.6–19.1)†	22.5 (21.4–23.2)*†	25.1 (19.3–30.0)*†‡	15.1 (13.4–16.0)	13.8 (12.2–14.6)
Minimum area, cm^2	8.0 (7.7–8.4)	11.4 (11.1–11.9)	15.0 (14.3–15.9)*†	17.0 (16.2–20.4)*†	18.9 (17.5–20.7)*†‡	27.3 (22.2–32.8)*†‡	9.7 (8.7–10.8)	11.2 (9.7–13.1)*
Minimum indexed area, cm^2/m^2	9.6 (9.1–10.2)	9.2 (9.0–9.7)	15.5 (14.5–17.2)*†	13.4 (10.9–14.4)*†	19.2 (17.8–20.6)*†‡	19.8 (15.2–27.7)*†‡	10.8 (10.3–11.6)	9.3 (8.0–10.7)
Reservoir function, %	64.0 (60.2–65.7)	63.4 (60.9–64.6)	32.5 (25.1–40.5)*	36.0 (27.9–45.2)*	16.2 (12.6–22.0)*†‡	20.8 (10.9–29.4)*†	37.2 (29.6–45.5)*	43.5 (34.0–58.0)
Conduit function, %	15.0 (14.9–15.2)	19.8 (17.7–22.8)	10.2 (7.1–14.4)	11.7 (8.1–14.9)	7.7 (6.2–9.7)*	8.7 (6.5–10.7)*	6.7 (2.1–12.4)*	10.7 (6.9–14.4)*
Booster function, %	27.2 (25.2–28.6)	22.7 (20.3–24.1)	15.9 (13.9–18.6)*	18.5 (15.8–19.6)	4.4 (2.4–9.9)*†	8.1 (5.6–15.4)*†	21.7 (17.1–24.8)	21.2 (19.3–24.9)

Values are median (interquartile range). For simplicity, baseline data for the LCx, LAI, and LAD experimental groups are not included. Pairwise comparisons at each time point. *$p < 0.05$ vs. control. †$p < 0.05$ vs. LAD. ‡$p < 0.05$ vs. LCx.

CMR = cardiac magnetic resonance imaging; LAD = left anterior descending; LAI = left atrial infarction; LCx = left circumflex artery.

and necrosis in the absence of other contributors, we induced anterior infarction by 45-min mid-LAD occlusion distal to first diagonal branch followed by reperfusion (LAD group) (14,15). This procedure produces consistent transmural infarction with LV dilation and systolic dysfunction (15).

CMR ACQUISITION PROTOCOL AND DATA ANALYSIS. CMR was performed at baseline (before MI) and at 1 and 8 weeks post-infarction, as previously reported (14) (see Online Appendix for detailed description).

LA volumes and function were defined as follows. Because no volumetric estimation methods have been validated in pigs, we quantified LA dimensions based on the mean area from the 4- and 2-chamber views. From these views, 3 phasic parameters were derived as follows.

1. Reservoir function or expansion index (%): 100 · (maximal LA area − minimum LA area)/minimum LA area
2. Conduit function (%): 100 · (maximal LA area − pre-atrial contraction area)/maximal LA area
3. Booster function (%): 100 · (pre-atrial contraction area − minimum LA area)/pre-atrial contraction area

Quantification of post-MI MR severity was performed in the LCx and LAI groups and in a subset of the LAD group (n = 4). The LV forward stroke volume (SV) was obtained from a phase-contrast sequence in the ascending aorta, and mitral regurgitant volume (RegVol) and regurgitant fraction (RF) were calculated as follows.

- CineSV = LV end-diastolic volume − LV end-systolic volume
- RegVol = forward SV − CineSV
- RF = RegVol/CineSV

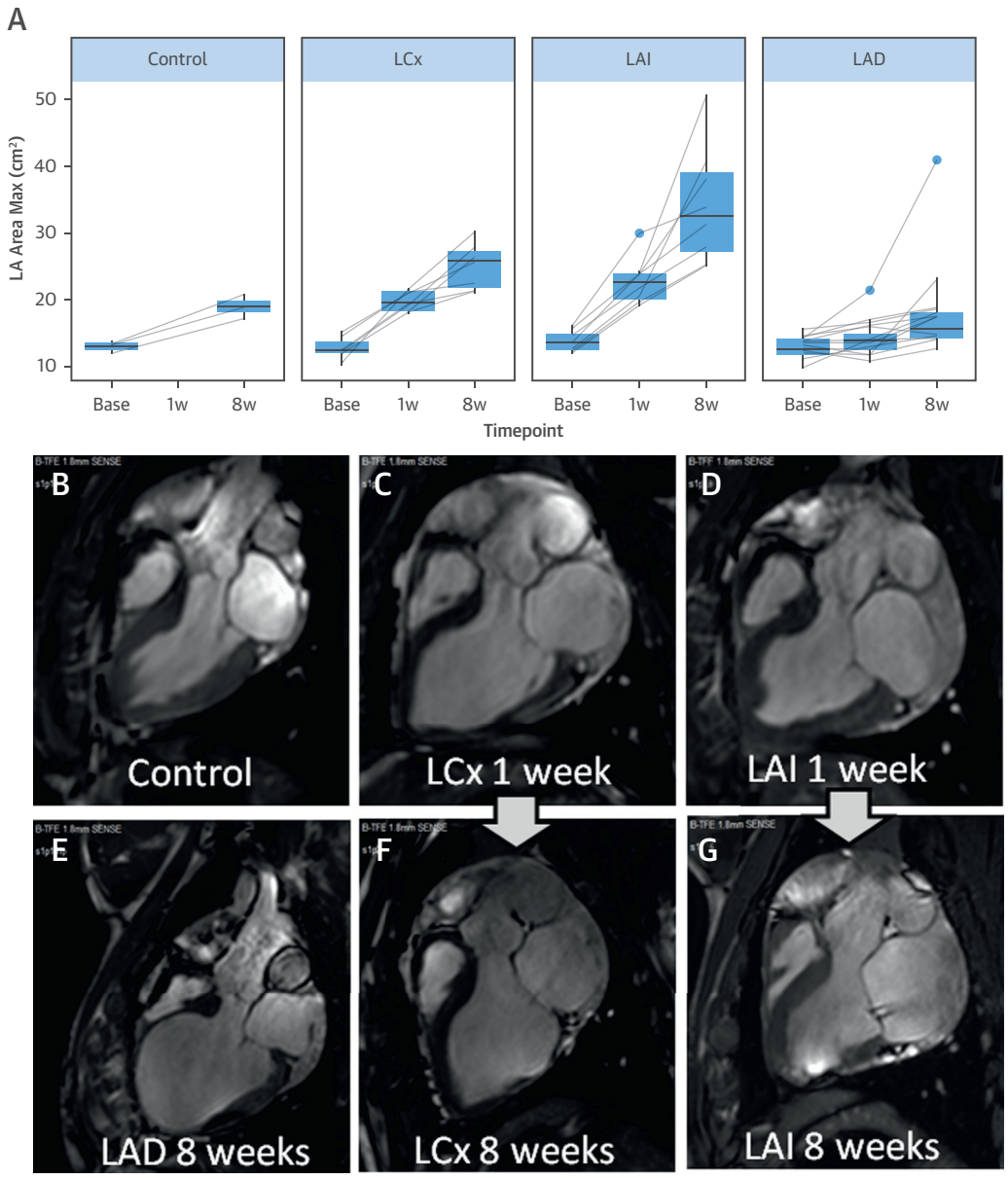
HISTOLOGY. After excision of the heart (at 1 week post-infarction in 2 pigs and at 8 weeks post-infarction in the remaining), tissue from the LA anterior wall was fixed in 10% neutral buffered formalin, embedded in paraffin wax, and cut into 4-μm sections. Picrosirius red-, hematoxylin-eosin-, and Masson's trichrome-stained sections were digitalized with a scanner (Nanozoomer-RS C110730, Hamamatsu, Photonics K.K.K., Hamamatsu City, Japan). Collagen organization was qualitatively evaluated using polarized light microscopy (Nikon ECLIPSE 90i, Nikon Corporation, Tokyo, Japan) on Picrosirius red-stained sections. Immunohistochemistry was performed to detect inflammatory cells in atrial tissue.

STATISTICAL ANALYSIS. Continuous variables are expressed as median (interquartile range). Between-group comparisons at each time point were performed using the nonparametric Kruskal-Wallis test followed by post hoc analysis corrected for multiple comparisons (Holm method). Associations between different parameters were evaluated using the Spearman's correlation coefficient. Statistical analyses were performed using R software version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was assigned at $p < 0.05$.

RESULTS

Data regarding the generation of MI models are provided in the Online Appendix. Final analyses were performed in data from animals that completed the

FIGURE 2 LA Remodeling After Infarction



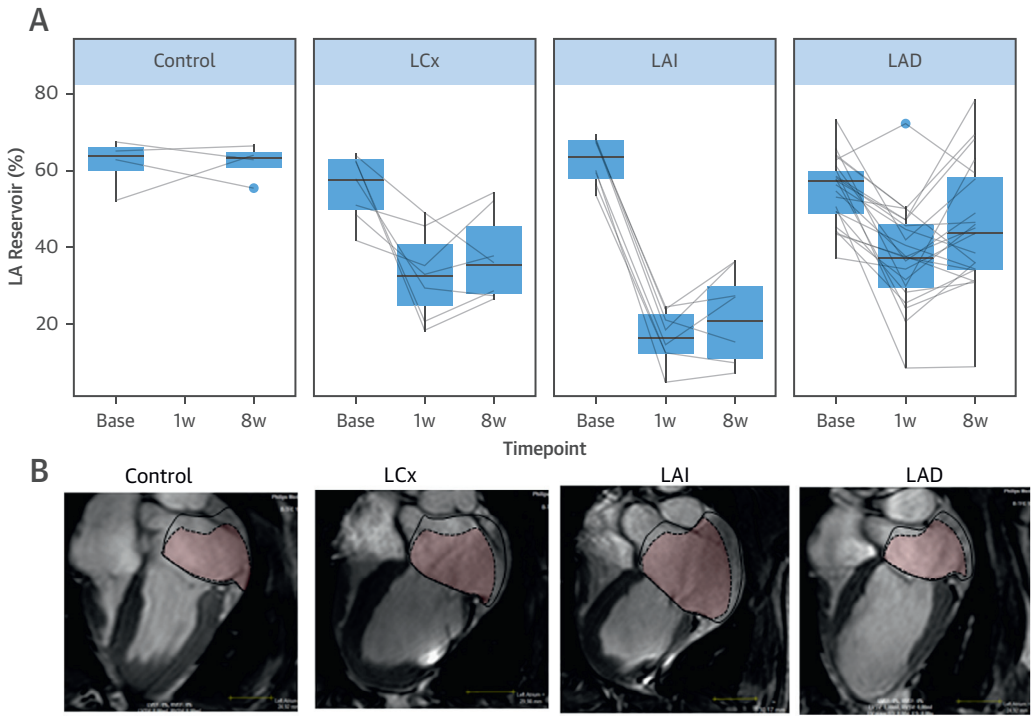
(A) Time course of maximum LA size for each group (presented as **boxplots and lines** for individual animals). **(B to G)** Representative images depicting end-systolic frames of the 3-chamber view in the group and time point indicated in each image. LA = left atrial; other abbreviations as in Figure 1.

study protocol (control group, n = 4; LCx group, n = 7; LAI group, n = 8; and LAD group, n = 21). Experimental procedures, study timeline, and groups are summarized in Figure 1.

TIME COURSE OF LA DILATION AFTER INFARCTION. LA dilation (at 1 week) was present in both groups of pigs undergoing LCx coil occlusion (LCx and LAI groups); however, dilation was larger in LAI pigs (Table 1, Figure 2). Moreover, LA dilation progressed faster in the LAI group from weeks 1 to 8. Interestingly, overall LA dilation was observed in the LAD group (compared with control pigs).

All 3 groups showed impaired LA reservoir function (reflecting LA compliance) at 1 week post-MI

FIGURE 3 **LA Reservoir Function Changes After Infarction**



(A) Time course of LA reservoir function for each experimental group. **(B)** Representative examples from the 8-week time point: images depict 4-chamber planimetry, with maximum area in **solid contours** and minimum area as **red-shaded and dashed contours**. Abbreviations as in Figures 1 and 2.

(Table 1, Figure 3). LA reservoir function was most prominently impaired in the LAI group (16.2% vs. 64.0% in controls, contrasting with 32.5% in the LCx group and 37.2% in the LAD group). At 8 weeks post-MI, the LCx and LAD groups showed a modest recovery in LA reservoir function (36.0% and 43.5%, respectively), whereas reservoir function in the LAI group remained weak (20.8%) (Table 1, Figure 3). Atrial contractility, measured as the booster pump function, followed a similar pattern, with the most prominent changes occurring in the LAI group (Table 1). Booster function in the LAI group was sharply reduced at 1 week post-MI (to 4.4%) and remained severely depressed at 8 weeks (8.1%). The LCx group showed more moderate reductions (15.9% at 1 week and 18.5% at 8 weeks), and the LAD group revealed the least reductions (21.4% at 1 week and 21.2% at 8 weeks). Within individual animals, a strong correlation was observed between reservoir and contractile properties (rho = 0.84; $p < 0.001$).

Atrial conduit function after acute MI was impaired to a similar extent in all groups, and no significant changes were observed between early and late follow-up (Table 1). This suggests that extrinsic factors other than LAI may influence impairment of this function, because LA conduit function is merely the transit of blood from the pulmonary veins to the LV. Interestingly, conduit function was the most prominently decreased component in the LAD group (Table 1).

TIME COURSE OF POST-INFARCTION LV DILATION AND FUNCTION. Table 2 summarizes the time course of CMR-determined LV structural remodeling and ischemic MR parameters in the experimental models. In all groups, post-MI LV remodeling was characterized by an enlarged LV and decreased LVEF. LV infarcts (quantified with a late gadolinium enhancement CMR sequence at 1 week) were significantly larger in the LCx and LAI occlusion groups (median infarct size 37.8% and 37.2%) than in the LAD group (28.1%). LV volume showed a similar pattern (Table 2).

At 1 week, significant modest linear associations were noted between LA dilation (maximal area) and LV infarct size (rho = 0.36; p = 0.02) and LV

TABLE 2 Time Course of LV Remodeling and Mitral Regurgitation Parameters by Study Groups

	Control (n = 4)		LCx (n = 7)		LAI (n = 8)		LAD (n = 21)	
	Baseline	8 Weeks	1 Week	8 Weeks	1 Week	8 Weeks	1 Week	8 Weeks
Body weight, kg	29 (29.0 to 29.4)	55.3 (53.5 to 57.1)	37 (35.0 to 40.0)*	70 (67.3 to 73.5)†	39 (34.8 to 43.0)*	62 (59.8 to 71.0)	35.0 (31.5 to 38.5)	53.5 (48.0 to 55.8)
LV								
Infarct size, % of LV mass	0	0	37.8 (27.2 to 39.9)*	18.0 (14.1 to 18.9)*†	37.2 (33.2 to 40.5)*	23.0 (16.7 to 27.9)*	31.6 (24.0 to 39.0)*	23.8 (21.7 to 31.1)*
EDV, ml	92.7 (86.9 to 98.8)	118.1 (112.5 to 125.5)	132.1 (121.9 to 142.1)*	242.5 (180.6 to 246.0)*	135.2 (121.1 to 141.8)*	202.9 (190.5 to 220.4)*	121.8 (112.0 to 133.9)*	183.2 (153.9 to 247.1)*
Indexed EDV, ml/m^2	111.7 (103.8 to 120.9)	96.6 (94.0 to 100.0)	137.3 (130.1 to 147.8)	161.5 (138.3 to 172.5)*	139.9 (129.8 to 143.2)	149.5 (145.4 to 154.4)*	134.6 (130.6 to 142.1)*	152.4 (135.3 to 179.7)*
ESV, ml	47.2 (43.3 to 50.4)	40.9 (38.3 to 43.5)	84.5 (69.3 to 91.5)*	121.4 (101.2 to 147.5)*	87.1 (75.4 to 90.6)*	128.0 (116.1 to 144.1)*	77.1 (66.3 to 85.4)*	131.1 (101.7 to 170.1)*
Indexed ESV, ml/m^2	56.9 (51.7 to 61.6)	33.1 (32.0 to 34.5)	90.1 (78.1 to 95.2)*	86.2 (76.7 to 101.7)*	88.2 (80.2 to 93.1)*	92.6 (87.9 to 101.3)*	86.1 (78.7 to 94.2)*	106.1 (89.6 to 124.8)*
LVEF, %	50.1 (49.4 to 50.8)	66.4 (64.0 to 68.1)	35.0 (34.6 to 38.1)*	47.3 (36.0 to 49.0)*†	36.7 (35.7 to 37.3)*	36.6 (33.0 to 40.1)*	36.4 (35.1 to 39.1)*	31.1 (29.0 to 33.8)*
Mitral regurgitation								
Regurgitant volume, ml	0.74 (−1.4 to 2.6)	1.2 (−0.4 to 2.1)	2.1 (1.9 to 4.0)	13.2 (8.7 to 16.6)	7.4 (5.8 to 11.1)	17.8 (15.5 to 27.2)	6 (4.0 to 8.0)	0 (0.0 to 3.0)
Indexed regurgitant volume, ml/m^2	0.9 (−1.7 to 3.4)	0.9 (−0.3 to 1.6)	2.2 (2.0 to 3.9)	9.6 (6.4 to 11.3)	7.5 (5.8 to 10.7)	13.8 (12.0 to 18.9)	6 (4.0 to 8.0)	0 (0.0 to 3.0)
Regurgitant fraction, %	1.4 (−3.3 to 5.5)	1.4 (−0.8 to 2.4)	4.3 (3.5 to 7.9)	15.6 (11.5 to 16.8)	17.2 (11.4 to 21.1)	25.1 (23.0 to 36.3)	10.7 (7.0 to 14.0)	0 (0.0 to 3.0)

Values are median (interquartile range). For simplicity, baseline data for the LCx, LAI and LAD experimental groups are not included. Pairwise comparisons at each time point *$p < 0.05$ vs. control. †$p < 0.05$ vs. LAD.

EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricle; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

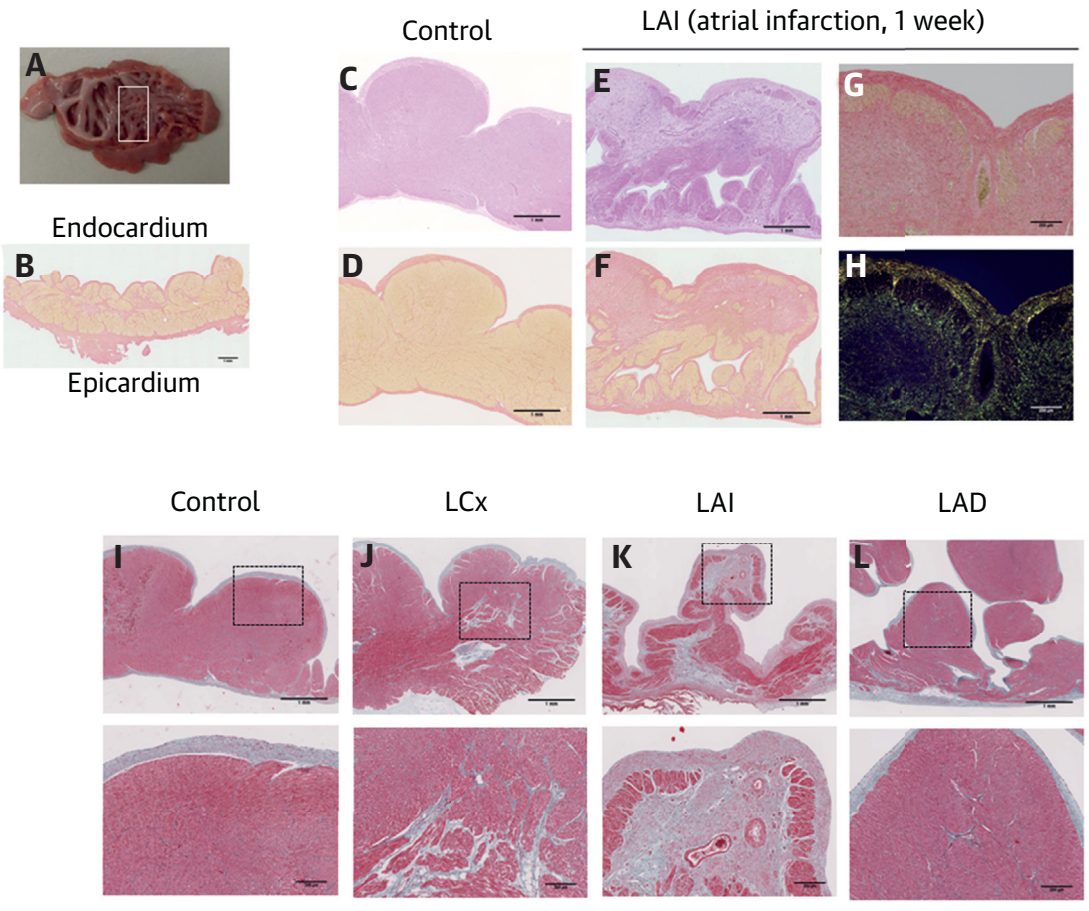
end-systolic volume (rho = 0.38; p = 0.01). These findings suggest that LV infarct size and LV end-systolic volume are not the only factors influencing post-MI LA dilation. Direct damage to the LA during LA branch occlusion may lead to larger LA volumes and more pronounced acute impairment of LA function. Subsequently, LV dilation and dysfunction together with MR would result in faster progression of LA remodeling and dysfunction in the LAI group than in the LCx and LAD groups.

DEVELOPMENT OF ISCHEMIC MR. Ischemic MR was measured from CMR-derived regurgitant volume and regurgitant fraction (RF) obtained at 1 and 8 weeks post-MI (Table 1). Ischemic MR was mild in the LCx group at 1 week (RF = 4.3%) but was more severe by 8 weeks (RF = 15.6%). In the LAI group, ischemic MR was even more pronounced at 1 week (RF = 17.2%) with further progression by 8 weeks (RF = 25.1%), showing a clear association with the early severe LA remodeling in this group. In the LAD subgroup of 4 assessed animals, ischemic MR observed at 1 week post-MI was mild and improved by the 8-week follow-up.

HISTOLOGICAL ANALYSIS OF POST-INFARCTION LA STRUCTURAL REMODELING. The effect of permanent LA branch occlusion on LA structure was evaluated in 2 additional animals undergoing the LAI procedure and sacrificed at 1 week. Compared with healthy atrial tissue from control animals, atrial tissue from LAI animals showed extensive myocardial injury, with cardiomyocyte loss and areas of fibrosis (**Figures 4C to 4H**), providing histological confirmation of the atrial infarction in this model. Qualitative assessment by polarized light microscopy revealed an immature collagen fiber organization in these areas, suggesting an early process of post-infarction repair in the LA myocardium.

Histological changes were assessed at 8 weeks post-MI in animals that completed the protocol. Atria were harvested immediately after the 8-week CMR. Extensive LA enlargement was observed in the LAI group (Online Figure 2). Atrial enlargement was associated with severe interstitial collagen deposition (**Figure 4,** Online Figure 3). Conversely, LA tissue from the LCx group was characterized by mild interstitial fibrosis. No pathological changes were observed in the LAD group, consistent with the absence of atrial dilation in this group in the CMR studies. Inflammatory cells were detected in the infarcted region at high number in the LAI group at 1 week, with progressive decline or even normalization at 8 weeks, compared with control tissue (Online Figures 4 and 5).

FIGURE 4 Histology of LA Remodeling



Representative examples of **(A)** atrial tissue and **(B)** a section with endocardium at the top and epicardium at the bottom. At 1 week post-MI, marked cardiomyocyte loss **(E)** with extensive fibrosis **(F to H)** was found compared with control subjects **(C and D)**. At 8 weeks post-MI, mild interstitial fibrosis was found in the LCx group **(J)** and severely fibrotic replacement in the LAI group atrium **(K)**, compared with the LAD group **(L)** and normal control subjects **(I)**. Scale bars = 1 mm in low magnification images and 200 μm in high magnification images. Abbreviations as in Figure 1.

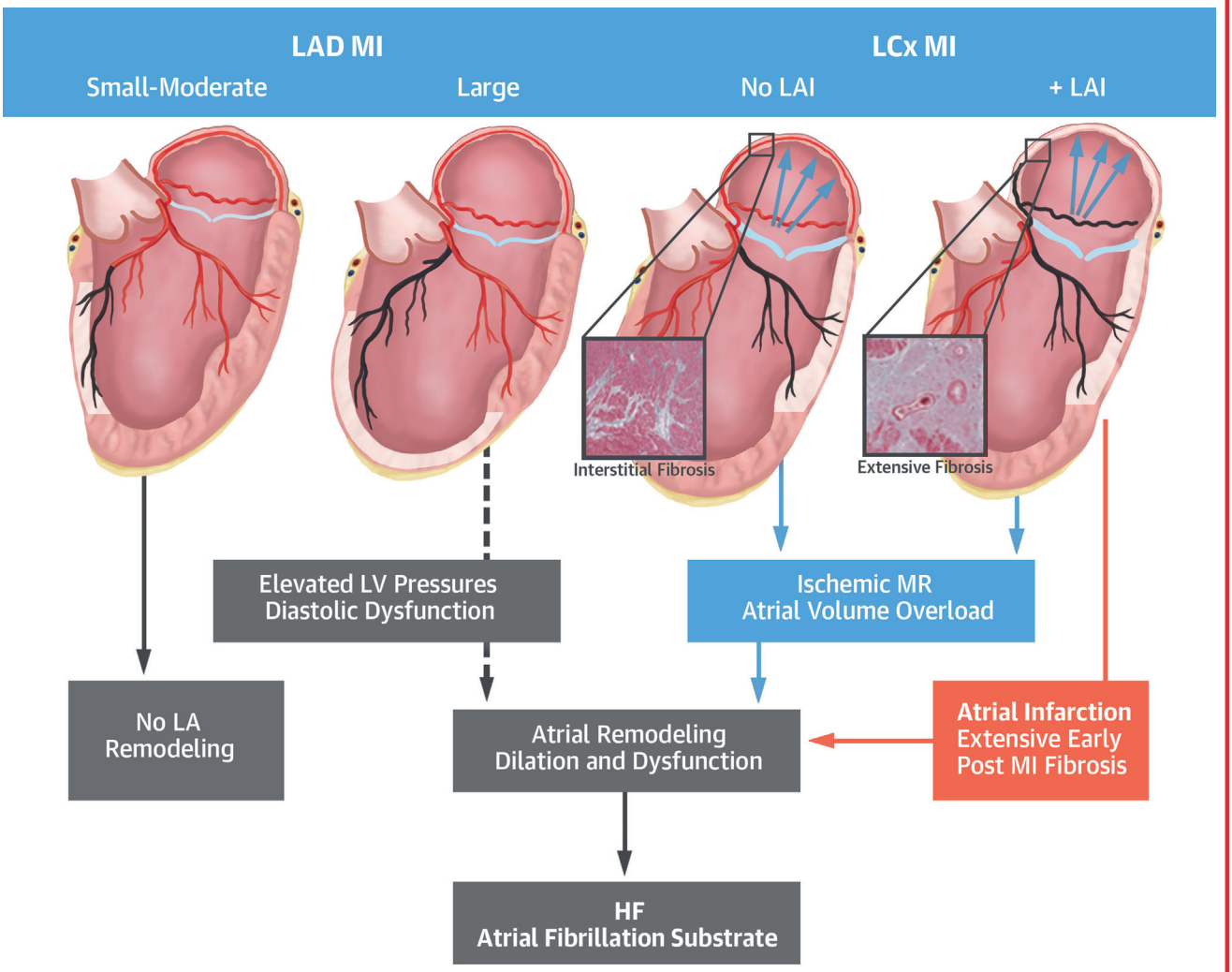
DISCUSSION

The present study provides insight into the determinants and consequences of LA remodeling in translational large animal models of acute MI (Central Illustration). The findings are as follows.

1. LAI complicating LCx-dependent infarction (LAI group) results in significant LA remodeling, with extensive scarring or fibrosis formation during the first week post-MI. These anatomical LA changes are associated with acutely and markedly altered reservoir and booster pump function and ischemic MR progression.
2. Ischemic MR without concomitant LAI (LCx group) is associated with early and progressive LA structural remodeling, although to a lesser extent than when associated with LAI (LAI group).
3. Post-MI LV dysfunction without ischemic MR or LAI is associated with mild, transient LA remodeling.

ATRIAL INFARCTION COMPLICATING ACUTE INFARCTION INDUCES SEVERE REMODELING AND PERSISTENT LA DYSFUNCTION. The most prominent finding of this study is the significant effect of LAI (secondary to LA proximal branch occlusion) on LA dilation and its persistent impairment of LA reservoir and booster pump functions. These functional abnormalities are related to extensive scar and fibrotic replacement of the atrial myocardium. The

CENTRAL ILLUSTRATION **Mechanisms of LA Remodeling After Acute MI**



Aguero, J. et al. J Am Coll Cardiol. 2017;70(23):2878–89.

LA mechanical and electrical remodeling occurs in some cases after acute MI. This remodeling is associated with increased risk of HF and susceptibility to atrial fibrillation. Cases in which the posterior LV wall is infarcted (e.g., left circumflex coronary artery occlusion), ischemic MR occurs because of leaflet retraction secondary to papillary muscle dysfunction. This increases LA pressure. In addition to this mechanism, when left circumflex coronary artery occlusion occurs at its very proximal segment, the LA branch can be occluded, resulting in LA necrosis. This mechanism plays a significant role in further contributing to atrial remodeling. Even in cases of MI not affecting mitral valve function primarily, the increase in LV pressures can result in "retrograde" increases in LA pressures, resulting in some degree of atrial remodeling. If the infarction does not affect the mitral valve function and is not large enough, no LA remodeling occurs. HF = heart failure; LA = left atrial; LAD = left anterior descending; LAI = left atrial infarction; LCx = left circumflex artery; LV = left ventricular; MI = myocardial infarction; MR = mitral regurgitation.

progression of LA chamber dilation and functional impairment from the subacute (1 week) to the chronic (8 weeks) phase identifies a specific time course of atrial myopathy. To the best of our knowledge, this is the first experimental evidence for the structural and functional effect of LAI, both in the early and late post-MI periods. In this regard, although atrial infarction diagnosis remains an unsolved challenge (10), autopsy reports suggest that the incidence is significant (11). The atrial coronary circulation system is complex (16), and the response of the atrial chamber to ischemia is poorly characterized. Prior studies showed that LA ischemia blunts the compensatory booster pump function during acute occlusion of the LA branch (17).

LAI secondary to permanent occlusion of the LA branch (LAI associated with proximal LCx occlusion)

resulted in severe atrial scarring and fibrosis due to replacement of extensive areas of cardiomyocyte loss. Collagen staining at 7 days post-MI revealed an immature structure. Conversely, at 8 weeks post-MI, a well-organized network with extensive interstitial distribution was observed. At this chronic stage, LA extracellular matrix remodeling was characterized by excessive collagen deposition. The net increase in collagen content likely contributes to the persistent, abnormal LA physiology, with marked blunting of reservoir and booster functions. This histological pattern in response to ischemic injury and the associated atrial structural remodeling (dilation and dysfunction) differs from previous reports, which showed varying degrees of atrial interstitial fibrosis in experimental models, including chronic atrial pacing, HF, and volume overload (18,19).

INTERPLAY BETWEEN LA STRUCTURAL REMODELING AND DEVELOPMENT OF ISCHEMIC MR. Our time course data indicate that LAI is a major determinant of early ischemic MR severity, with a much higher RF in the LAI group at 1 week post-MI (15% vs. 4% in the LCx group). Interestingly, at this time point, the LCx group had a similar extent of LV structural injury assessed by infarct size, LV volume, and LVEF, suggesting that the mitral subvalvular apparatus was similarly affected in the LAI and LCx groups. This conclusion is supported by the similar progression of ischemic MR from early (1 week) to late (8 weeks) follow-up in these groups (RF increasing from 7.9% to 11.3%) (**Table 1**), suggesting that progressive LV remodeling is the driving mechanism. Ischemic MR is defined as a consequence of chronic LV remodeling and changes to the mitral subvalvular apparatus, typically occurring 2 weeks after acute MI (20). Based on our observations, we propose that in the LAI group, scarring after direct damage to the LA would lead to early LA dilation and dysfunction. This LA remodeling may alter the mitral valve geometry by inducing mitral annulus dilation (Online Results, Online Table 1), resulting in leaflet malcoaptation and MR. Subsequent LV remodeling may lead to faster progression of LA dilation and dysfunction, with larger mitral regurgitant volumes than in the other groups.

CONTRIBUTION OF LV INJURY TO LA REMODELING AFTER ACUTE INFARCTION. At 1 week post-MI, there was only a moderate correlation (correlation coefficient ~0.4) between CMR-assessed LV remodeling (estimated from ESV or infarct size) and LA remodeling. In our experimental setting, this weak correlation was due to the absence of overall LA dilation in most animals in the LAD group and the intrinsic LA injury effect in the LAI group. Interestingly, clinical studies show that the LV dimensions are larger in patients with early LA dilation (3–5), but the linear correlation between LV and LA parameters is poor (21), indicating a significant role for other factors, such as clinical history.

The lack of LA dilation in most animals in the LAD group was an unexpected study finding. Our study design could not answer whether larger LAD infarcts (seen in individual cases) (**Figure 2**) or longer follow-up periods would have eased the detection of LA remodeling; however, this is suggested by prior experimental reports (22). In general, infarct size was smaller in the LAD group versus the LCx and LAI groups (37.8% vs. 37.2% and 31.6%, respectively) (**Table 2**), probably due to differences in the site and duration of coronary occlusion (mid-LAD ischemia-reperfusion vs. chronic proximal LCx occlusion). The absence of structural LA remodeling was supported by the absence of fibrosis in the histological analysis. LA remodeling was not comprehensively characterized in previous experimental models. Chamber dilation has been described in very large, proximal LAD infarctions after 3 months of follow-up (22) and in the rat model of post-MI HF (23), whereas most ischemic MR models focused on valve geometry rather than LA remodeling (7,24–26). Finally, atrial function changes in the LAD group (decreased conduit and reservoir function) may be explained by impaired LV function by mechanisms previously described (27), because no histological abnormalities were found.

In the present study, time course assessment of LA structural remodeling (dilation, dysfunction, and histology) provided novel insights into the role of fibrosis. Although intrinsic atrial injury due to infarction (LAI group) produced early dilation and persistent functional impairment, there was some degree of improvement in reservoir function (LAI group vs. LCx group) (**Figure 3**). This suggests that factors other than fibrosis may affect LA function in this setting, such as atrial stunning. Large clinical series suggest that the late progression of LA remodeling parameters (LA dimensions or reservoir function) is only weakly predicted by baseline LV or LA imaging parameters obtained during early post-MI assessment (4,28–29).

Clinical studies indicate that both LA remodeling and ischemic MR predict long-term

outcome independently of LV remodeling parameters (3-5,8,21,28,30,31). A plausible explanation is the development of pulmonary hypertension as a consequence of increased LA pressures. Supporting this explanation, in our preliminary observations, LA remodeling parameters and ischemic MR severity both correlated with pulmonary hemodynamics in the LAI and LCx groups (Online Appendix, Online Table 2, Online Figures 6 and 7).

The present study provides evidence of the effects of atrial infarction during acute MI on the LA remodeling process. In this regard, recent data suggest that atrial coronary occlusion is a relatively frequent (~15%) complication of percutaneous coronary intervention and entails a markedly higher risk of atrial arrhythmias (10), confirming previous experimental observations that linked acute LA ischemia to greater arrhythmia vulnerability (32-34).

STUDY LIMITATIONS. The LCx occlusion induced to model atrial ischemia entailed severe LV remodeling and ischemic MR, limiting our ability to isolate the contribution of each component. We did not specifically investigate the contribution of distal LCx branches (that may have induced posterior LA wall ischemia) or proximal right coronary artery branches to left atrial perfusion (35).

The lack of hemodynamic measurements at the early stage, including LV end-diastolic or LA pressures limits our understanding regarding the absence of atrial remodeling in the LAD group. However, in previous studies (17,36), both LV end-diastolic and LA pressures increased acutely to a similar extent in both LAD and LCx coronary occlusions, but LA function was only impaired in the LCx group. Although these studies support the notion that proximal LCx occlusion impairs LA function due to LA ischemia, they lacked follow up surveillance of atrial remodeling and histology changes.

We did not investigate ECG changes nor quantify the atrial infarction size by CMR, and future translational studies are warranted to evaluate such atrial involvement by noninvasive diagnostic strategies.

CONCLUSIONS

The current study provides the first experimental evidence of the structural effect of LAI after acute MI. In addition to acute LA dilation, major features of this entity are severe and persistent atrial function impairment and extensive fibrosis. Acute atrial dilation and dysfunction contribute to the early occurrence of ischemic MR, whereas ischemic MR progression further affects atrial structural remodeling through a complex interplay.

ACKNOWLEDGMENTS The authors thank Roisin Doohan for processing myocardial tissue samples for histological analysis; Tamara Córdoba and Oscar Sanz for their animal care work; the Veterinary Unit supervision of Rubén Mota and Nuria Valladares; Santiago Rodriguez and Eugenio Fernández of the CNIC animal facility and farm; and Simon Bartlett for his English editing.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: After acute MI, remodeling of the LA carries an unfavorable prognosis. Occlusion of the circumflex coronary artery proximal to the origin of the LA branch causes atrial infarction, followed by early LA remodeling, enlargement, and extensive atrial fibrosis, and then by progressive ischemic MR.

TRANSLATIONAL OUTLOOK: Further studies are needed to relate post-infarction LA remodeling and resulting mitral valve function to left heart hemodynamics and findings obtained by multimodality imaging.

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KEY WORDS atrial fibrosis, atrial infarction, experimental model, mitral regurgitation, myocardial infarction

APPENDIX For expanded Methods and Results sections as well as supplemental tables and figures, please see the online version of this article.