

## Myocardial Infarction and Atrial Fibrillation Importance of Atrial Ischemia

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**Background**—Myocardial infarction (MI) is associated with the development of atrial fibrillation (AF). We aimed to characterize the atrial abnormalities because of MI and determine the role of ischemia to the AF substrate.

**Methods and Results**—Forty-four sheep were studied. MI was induced by occlusion of the left circumflex artery (LCX) or left anterior descending artery (LAD). Excluding 11 with fatal arrhythmias, equal groups of animals (LCX; LAD; and sham-operated) underwent sequential electrophysiology study for 45 minutes to determine atrial effective refractory periods, conduction velocity, conduction heterogeneity index, and AF inducibility. Postmortem evaluation was performed with 2,3,5 triphenyl tetrazolium chloride staining. MI resulted in greater left ventricular dysfunction ( $P < 0.05$ ), LA pressure ( $P < 0.0003$ ), and reduction in atrial effective refractory periods ( $P < 0.0001$ ) compared with control. 2,3,5 triphenyl tetrazolium chloride staining demonstrated that the left circumflex artery, and not the LAD, group had atrial infarction. The left circumflex artery group demonstrated the following compared with the LAD or control groups: greater slowing in atrial conduction velocity ( $P < 0.0001$  and  $P < 0.001$ ); increased absolute range of conduction phase delay ( $P < 0.001$  and  $P < 0.001$ ); increased conduction heterogeneity index ( $P < 0.0001$  and  $P < 0.001$ ); greater AF vulnerability ( $P < 0.05$  for both); and longer AF duration ( $P < 0.05$  for both). LAD group had modest but significant slowing in conduction velocity ( $P < 0.01$ ) but no change in conduction heterogeneity index or AF duration compared with control.

**Conclusions**—Left ventricular infarction, which is known to result in atrial stretch, hemodynamic change, and neurohumoral activation, contributes partially to the atrial abnormalities in MI. Atrial ischemia/infarction results in greater atrial electrophysiological changes and propensity for AF forming the dominant substrate for AF in MI. (*Circ Arrhythm Electrophysiol.* 2013;6:738-745.)

**Key Words:** acute coronary syndrome ■ atrial fibrillation ■ myocardial infarction  
■ myocardial ischemia ■ remodeling

Atrial fibrillation (AF) remains common in the setting of myocardial infarction (MI) despite the increasing use of early reperfusion strategies.<sup>1-5</sup> When AF occurs after MI, it tends to recur in >20% during follow-up.<sup>1,6</sup> Although the prognostic significance of AF after MI is well-established,<sup>2-4,7,8</sup> the mechanism for this heightened risk is not fully understood. The relative contribution of atrial ischemia, ventricular dysfunction, hemodynamic changes, and neurohumoral abnormalities to the development of AF after MI has not been evaluated.

### Clinical Perspective on p 745

The role for atrial ischemia/infarction in the pathogenesis of AF after MI has been suggested.<sup>9</sup> Atrial infarction has been observed in 17% of MI patients in a large postmortem study.<sup>10</sup> In addition, an increased risk of atrial tachyarrhythmia has

been observed in patients with atrial infarction.<sup>11,12</sup> In a post-mortem series, James and Burch<sup>13</sup> demonstrated that atrial infarction was present in all MI cases that developed atrial tachyarrhythmia. The human left atrium (LA) gets its blood supply from the sinoatrial branch that arises from the right coronary artery in 50% to 60% of the cases or the left circumflex artery in 40% to 50% of the cases.<sup>13</sup> In addition, there are LA branches, which arise from the proximal part of the left circumflex artery. Coronary artery disease, involving the atrial branches, is associated with higher incidence of new onset AF after MI.<sup>12,14-16</sup>

In sheep, the left circumflex coronary artery (LCX) is the dominant coronary arterial supply to the atria. In contrast, although the left anterior descending (LAD) supplies an equivalent extent of the ventricular myocardium, it does not have a major contribution to the atria.<sup>17</sup> This anatomic difference in

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blood supply provides a unique model to evaluate the role of atrial ischemia/infarction. In this study, we induced acute MI in an ovine model to understand the mechanism by which MI results in the substrate for AF. In particular, by evaluating the differences in LCX and LAD infarction, we aimed to determine the contribution of atrial ischemia/infarction in creating the AF substrate while controlling for other perpetrators, such as atrial stretch, hemodynamic change, and neurohumoral activation.

## Methods

Forty-four Merino Cross Wethers with a weight of  $56 \pm 8$  kg were studied (Figure 1). After acclimatization, animals were allocated to either MI (equally with LAD and LCX occlusion) or control (Sham-operated) group. All procedures were conducted in accordance with the guidelines outlined in the Position of the American Heart Association on Research Animal Use. Approval for the performance of the study was provided by the Animal Ethics Committees of the University of Adelaide and SA Pathology, Australia.

### Study Protocol

All procedures were performed under general anesthesia. Sodium thiopental (15–20 mg/kg) was used for induction to facilitate endotracheal intubation and isoflurane (2% to 4%) in 100% oxygen was used for maintenance. Invasive blood pressure, heart rate, LA pressure (LAP), end-tidal  $\text{CO}_2$ , oxygen saturation, and temperature were continuously monitored throughout the study protocol.

### Myocardial Infarction

MI was induced by percutaneously cannulating the left coronary system using a guiding sheath (AL1; Boston, MA) and then inflating a angioplasty balloon (Voyager NC, Abbott Group). The angioplasty balloon was sized and inflated to achieve a total occlusion of either the LAD or LCX vessels. Among 44 animals, 11 developed fatal arrhythmia

without completion of the study and were, therefore, excluded. The remaining 33 animals were equally divided into 3 groups: occlusion of proximal-LCX ( $n=11$ ; to induce left atrial ischemia/infarction in addition to left ventricular infarction); occlusion of proximal LAD ( $n=11$ ; left ventricular [LV] infarction with no atrial ischemia/infarction); and 11 sham-operated controls animals undergoing the identical protocol without MI. The angioplasty balloon was kept inflated for 45 minutes and acute ischemia was confirmed on surface ECG.

The left ventricular ejection fraction was assessed using echocardiography at baseline and 30 minutes after balloon inflation. The presence of infarction was identified by staining with 2,3,5 triphenyl tetrazolium chloride.<sup>18–20</sup>

### Electrophysiology Study

Open chest electrophysiological studies were performed. Using a limited pericardiectomy, a custom designed 64-electrode plaque with 5 mm interelectrode distance was applied to the LA. Surface ECG and overlapping bipolar electrograms were continuously monitored and stored for off-line analysis using a computerized recording system (LabSystem Pro, Bard Electrophysiology, Lowell, MA). Electrograms were filtered from 30 to 500 Hz and measured with computer-assisted callipers at a sweep speed of 200 mm/s. Electrophysiological evaluation was performed at 15-minute intervals until the termination of the procedure. The following parameters were determined at each time point:

#### Atrial Refractoriness

Left atrial effective refractory periods (ERP) was measured by pacing from one prespecified corner of the plaque at twice diastolic threshold at cycle lengths of 400 and 250 ms. A single extrastimulus (S2) was introduced after 8 basic stimuli (S1) starting with a coupling interval of 300 ms and reducing in 10 ms decrements until loss of capture. Atrial ERP was defined as the longest S1-S2 interval not resulting in a propagated response. The ERP was measured 3× at each cycle lengths at each time point, and if the maximum and minimum differed by >10 ms, 2 additional measurements were taken and the total was averaged.

#### Atrial Conduction

Conduction was assessed during stable S1-pacing at 400 and 250 ms. Activation maps were created using semiautomated custom-made software.<sup>21,22</sup> Each annotation was manually verified with the local activation time annotated to the peak of the largest amplitude deflection on bipolar electrograms. Local conduction velocity was calculated from the local vectors within each triangle of electrodes as previously described.<sup>21,22</sup> A mean conduction velocity can then be derived.

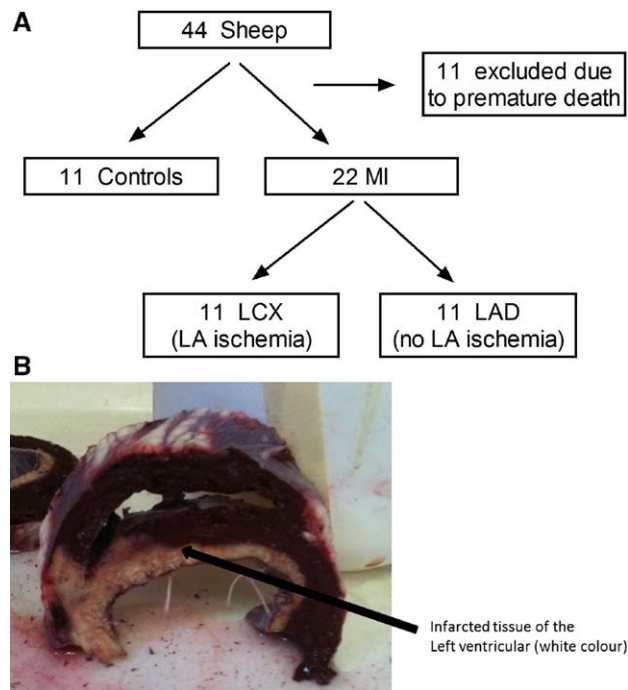
Conduction heterogeneity was assessed using phase-mapping techniques during S1-pacing.<sup>23</sup> In brief, the largest activation time difference between every 4 adjacent electrodes was first determined and divided by interelectrode distances. The largest value at each site was then used to create a phase map, with values also displayed as a histogram. Absolute conduction phase delay was calculated by subtracting the 5th from 95th percentile (P5-95). The conduction heterogeneity index was calculated by dividing the absolute phase delay by the median (P50). The conduction heterogeneity index is used to evaluate the heterogeneity in conduction in the atrial tissue.

#### AF Vulnerability

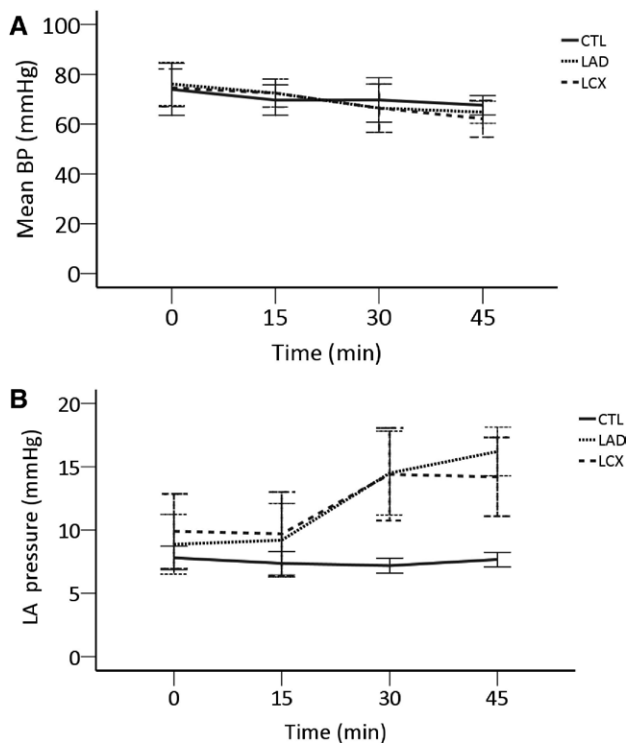
The inducibility and duration of AF were evaluated using programmed extra stimuli during ERP testing. Induced AF was documented with percentage of inducibility taken as the number of AF episodes over the total number of S1-S2 drive. AF was defined as a rapid irregular atrial rhythm of  $\geq 2$  s. Mean duration of AF episodes were derived from the average of all induced episodes in each group. Sustained AF was defined as arrhythmia of >10 minutes duration. If AF was sustained, no further data were collected.

### Statistical Analysis

Data analysis were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). All continuous variables are reported as mean $\pm$ SD



**Figure 1.** **A**, Summary of the study design. **B**, Infarcted tissue (red arrow) in left anterior descending artery territory (LAD) high-lighted using 2,3,5 triphenyl tetrazolium chloride staining. LA indicates left artery; LAD, left anterior descending artery; LCX, left circumflex artery; and MI, myocardial infarction.



**Figure 2.** **A**, Hemodynamic changes of the 3 groups (LCX, LAD, and control) over 45 minutes. It showed no hemodynamic differences between the groups over time. **B**, Left atrial pressure (LAP) changes over time in the 3 groups (LCX, LAD, and control). It shows a significant increase in LAP in MI group compared with control. Meanwhile, there was no difference in LAP between LCX and LAD. BP indicates blood pressure; CTL, control; LA, left atrial pressure; LAD, left anterior descending artery; LCX, left circumflex artery; and MI, myocardial infarction.

and assessed for normality using the Shapiro–Wilk test. The changes in hemodynamic were assessed using an ANOVA. To compare changes in the outcome measures among the 3 treatment groups, a linear mixed effects model was fitted to the data. In the model, treatment group, time, and the interaction between treatment group and time were fitted as fixed effects, whereas animal was fitted as a random effect. The changes in the electric properties were assessed at 0, 15 minutes, 30 minutes, and 45 minutes after balloon inflation. Kruskal–Wallis test was used to compare AF duration between the groups. Because of high variation or overdispersion of AF incidence data among the groups over 45 minutes, negative binomial regression was used to compare AF incidence between the groups. Statistical significance was established at  $P < 0.05$ .

## Results

A total of 33 animals were studied in the following groups: LCX occlusion ( $n=11$ ; ventricular and atrial ischemia/infarction); LAD occlusion ( $n=11$ ; ventricular infarction alone); and control ( $n=11$ ; sham-operated; Figure 1). At the end of the study, 2,3,5 triphenyl tetrazolium chloride staining demonstrated that the LCX, and not the LAD group or the controls, had atrial infarction (LCX 11 versus LAD 0;  $P < 0.05$  and LCX 11 versus control;  $P < 0.05$ ).

### Hemodynamic and Heart Rate Changes

Figure 2 demonstrates the hemodynamic changes seen in each group. There was no significant difference between the groups in mean arterial blood pressure over time. The left

ventricular ejection fraction (LVEF) was similar between the groups at baseline (LCX versus LAD versus control:  $60 \pm 4$  versus  $61 \pm 3$  versus  $62 \pm 5\%$ ;  $P = \text{ns}$ ). There was a significant reduction in LVEF in the 2 MI groups 30 minutes after balloon inflation compared with control (LAD  $37 \pm 2.7\%$  [ $P = 0.0002$ ]; and LCX  $36 \pm 4\%$  [ $P = 0.0001$ ]); however, there was no significant difference in LVEF between MI groups ( $P = 0.2$ ). In keeping with reduction of LVEF, there was significant increase in LAP in MI groups compared with control (LCX:  $P < 0.001$ ; and LAD:  $P < 0.001$ ; Figure 2A). Importantly, this increase in LAP demonstrated no difference between the LCX and LAD groups ( $P = 0.2$ ).

There was no difference in heart rate between the groups at baseline ( $P = 0.6$ ; Figure 2B). However, with MI, animals in both MI groups became more tachycardic compared with control at 30 minutes after balloon inflation (LCX versus control [ $P = 0.02$ ]; LAD versus control [ $P = 0.03$ ]). There was no significant difference in heart rate between LCX and LAD over time ( $P = 0.5$ ).

### Atrial Electric Changes Because of MI

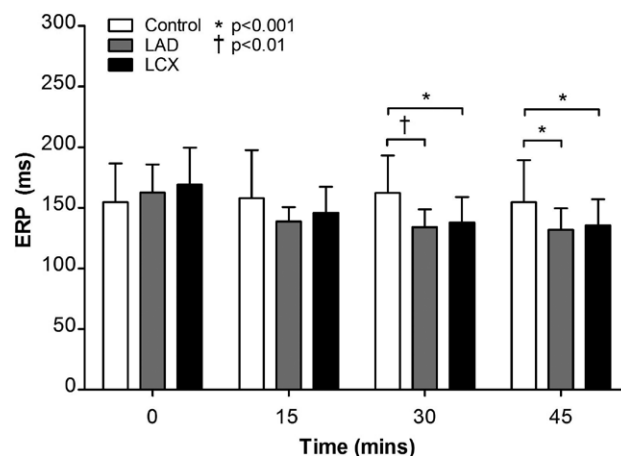
#### Effective Refractory Period

The left atrial ERP shortened in both MI groups compared with control ( $P = 0.004$ ); however, there was no significant differences between the MI groups ( $P = 0.6$ ). The reduction in ERP was observed as early as 15 minutes but became statistically significant 30 minutes after MI (Figure 3).

#### Conduction Velocity

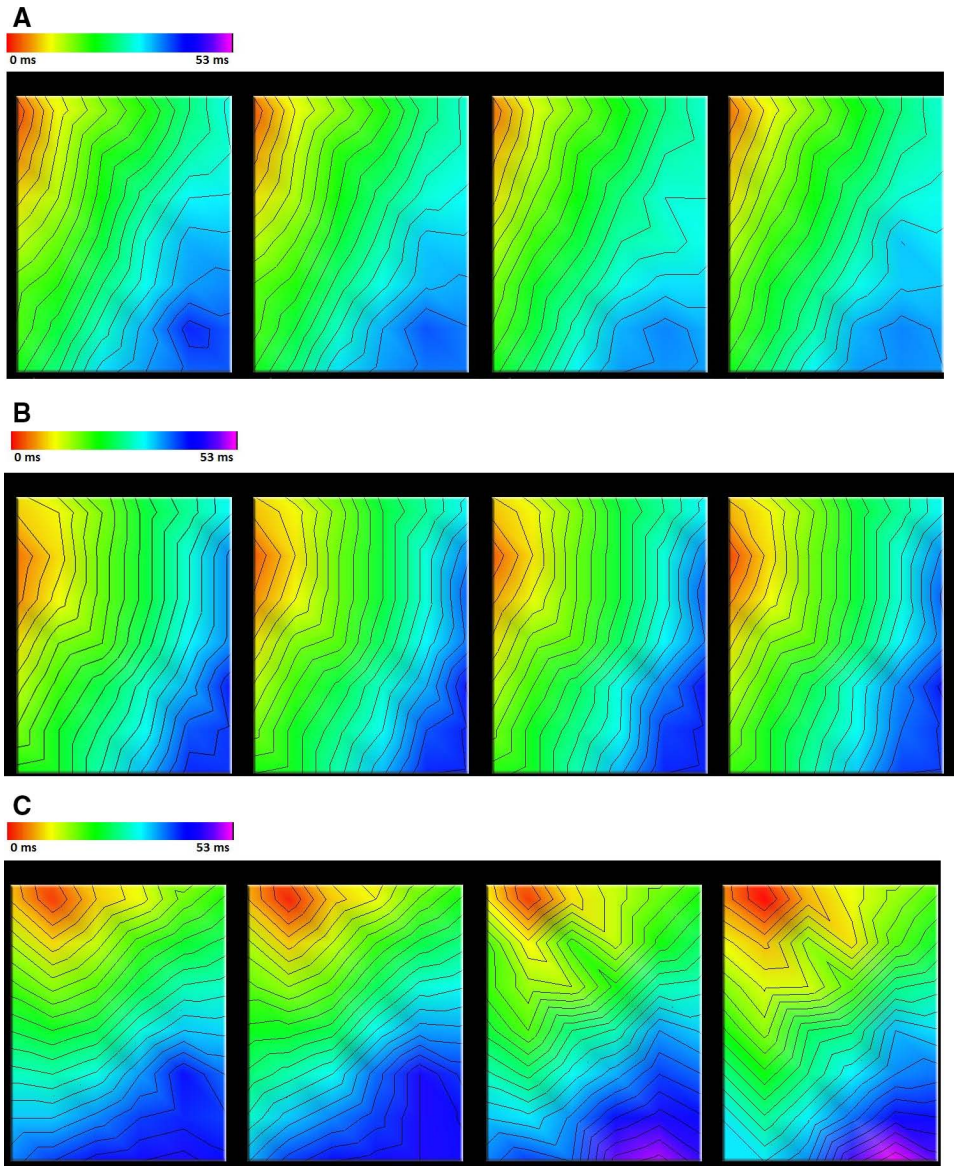
Figure 4 demonstrates representative examples of activation maps in each group. Activation contours drawn at equal time intervals highlight areas of isochronal crowding. This figure demonstrates that although there are some changes observed in the LAD group, the most marked impact on conduction was in the LCX group.

With MI, there was a reduction in atrial conduction velocity (Figure 5). LV infarction alone, as observed in the LAD group,



**Figure 3.** Changes in atrial effective refractory periods (ERP) at cycle length 400 ms over 45 minutes after balloon inflation. There was a significant reduction ERP over time, which started as early as 30 minutes and persisted in myocardial infarction groups (LCX and LAD) compared with control ( $P = 0.004$ ). There was no significant difference between LCX and LAD groups. LAD, left anterior descending artery; and LCX, left circumflex artery.





**Figure 4.** Representative activation maps from each group at 15-minute intervals for the study duration at a cycle lengths of 400 ms. Each map has used fixed scale (0–53 ms) to facilitate comparison between the groups. **A**, Control group showing normal conduction with no isochronal crowding. **B**, LAD group showing a slight reduction in CV but no significant isochronal crowding. **C**, LCX group with atrial ischemia showing slowing in conduction velocity and isochronal crowding with susceptibility to reentry. CTL indicates control; CV, conduction velocity; LAD, left anterior descending artery; and LCX, left circumflex artery.

induced a modest but significant change in conduction compared with control ( $P=0.01$ ). However, with additional atrial ischemia as observed in the LCX group, there was marked and progressive slowing of conduction compared with LAD ( $P<0.001$ ) or control ( $P<0.001$ ).

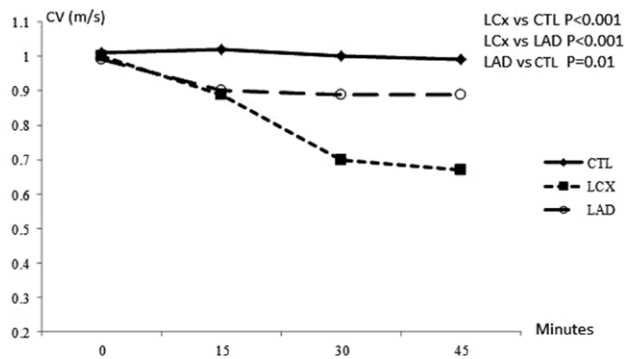
There was also evidence of significant increase in conduction heterogeneity as reflected by the absolute range of conduction phase delay (p5-95, expressing the total range in maximal differences in activation time) and the conduction heterogeneity index (to express the heterogeneity of conduction, overall mean P5-95/P50; Figure 6). The absolute range of conduction phase delay was increased in the LCX group compared with LAD ( $P<0.001$ ) or control ( $P<0.001$ ; Figure 6A). The conduction heterogeneity index was markedly increased in the LCX group compared with LAD ( $P<0.0001$ ) or control ( $P<0.001$ ; Figure 6B). There were no differences in these parameters of conduction heterogeneity over time in the LAD and control groups.

#### AF Vulnerability

Figure 7A shows the number of AF events by group. The AF incidence rate ratio (IRR) was significantly higher in LCX compared with LAD (LCX versus LAD, IRR, 6 [2–18];  $P=0.001$ ) or control group (LCX versus control, IRR, 12 [3.26–44.14];  $P<0.001$ , negative binomial model). In contrast, there was no significant differences in IRR between the LAD and control groups (IRR, 2 [0.47–8.5];  $P=0.4$ ). In addition, when AF developed, it persisted for a significantly longer duration in LCX group compared with LAD or control groups ( $P<0.05$ ; Figure 7B). Three (27%) in LCX groups developed sustained AF, whereas this was not observed in the other groups.

#### Discussion

This study provides new information on the relative contribution of atrial ischemia/infarction to the development of the substrate for AF associated with MI. Using the ovine coronary circulation, that has differential blood supply to the atria



**Figure 5.** Conduction velocity with time in each of the groups. The marked and progressive slowing in conduction velocity (CV) in LCX group compared with LAD or control is demonstrated. There was modest reduction in CV in LAD group compared with controls. CTL indicates control; LAD, left anterior descending artery; and LCX, left circumflex artery.

(supplied by the LCX) but equal supply to the ventricle from the LAD and LCX, it demonstrates that:

1. Atrial ischemia is the important determinant for the development of the AF substrate during MI. This is characterized by slowed and heterogeneous conduction. These abnormalities were independent of LV function or

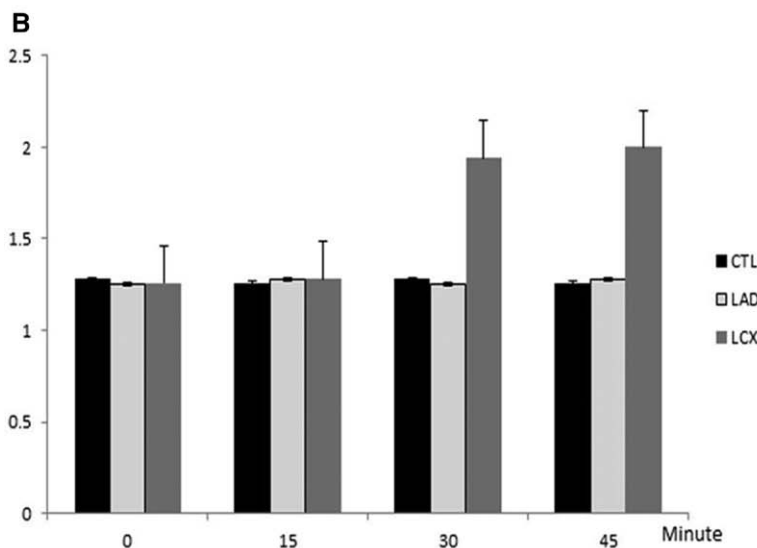
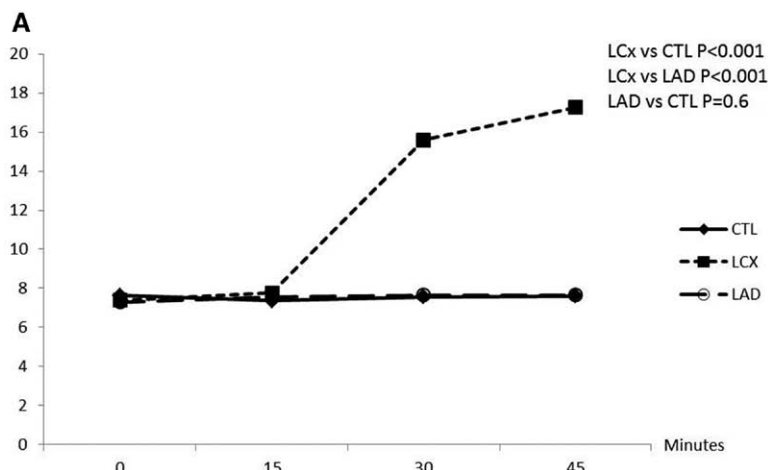
the hemodynamic changes that occur during the acute phase of MI. As a result of these abnormalities, not only AF was more frequently induced, but it also more frequently became sustained.

2. Acute MI, independent of atrial ischemia, results in significant hemodynamic changes and atrial stretch. These factors were associated with the abbreviation of ERP but only modest change in the conduction properties of the atria.

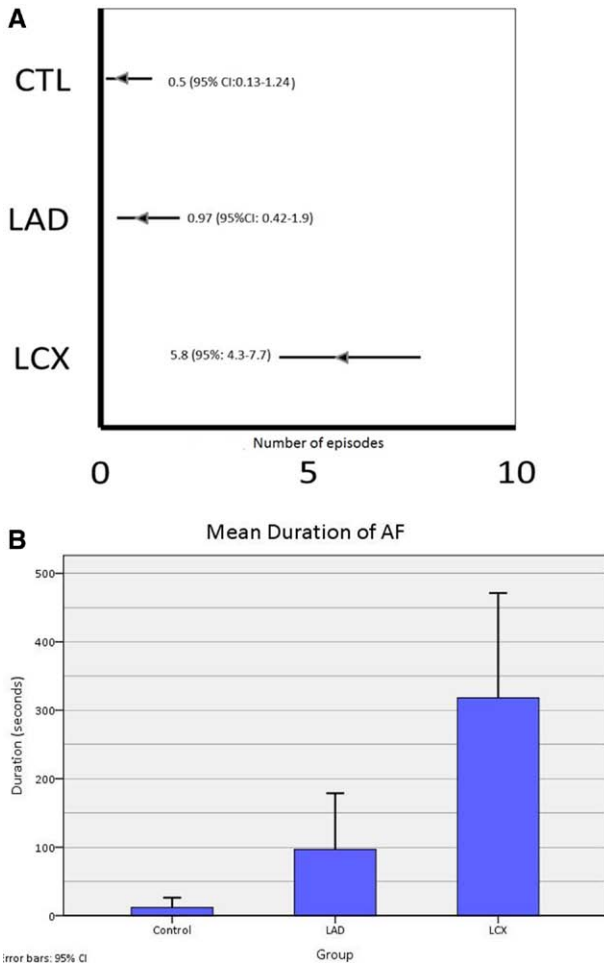
Although the incidence of AF and its prognosis after MI has been extensively studied,<sup>2-4,7,8,24</sup> data on AF pathophysiology after MI is limited.<sup>9</sup> To our knowledge, no previous study has evaluated the relative influence of factors associated with acute MI that contribute to the AF substrate.

### Ventricular Infarction, Atrial Stretch, and the Hemodynamic Changes

Ventricular infarction in both LCX and LAD groups resulted in comparable moderate LV dysfunction with similar changes in heart rate and blood pressure with early and persistent rise in LA pressure. As such, the electromechanical response to ventricular infarction would be of a similar intensity in both groups. This was associated with equivalent significant reduction in ERP in both



**Figure 6. A,** Absolute inhomogeneity of conduction (P5-95). The LCX group demonstrates marked and progressive changes compared with LAD or control. This was evident 15 minutes after angioplasty balloon inflation in LCX. **B,** Conduction heterogeneity index significantly increased over 45 minutes (15 minutely intervals) in LCX group compared with LAD or control. The result was evident 30 minutes after myocardial infarction. CI indicates confidence intervals; CTL, control; LAD, left anterior descending artery; and LCX, left circumflex artery.



**Figure 7. A**, Number of atrial fibrillation (AF) episodes in each group during effective refractory periods testing. This was significantly higher in LCX groups compared with LAD or control. There was no difference in AF inducibility between LAD and control. **B**, Mean duration of all induced AF in each group (seconds). This was significantly longer in LCX compared with control or LAD. CI indicates confidence intervals; LAD, left anterior descending artery; and LCX, left circumflex artery.

MI groups. In addition, the acute LA stretch resulted in a modest slowing in conduction velocity (with proximal LAD occlusion). These findings are consistent with previous animal studies showing that electromechanical feedback is produced by activation of stretch activated channels, which can effect both inward and outward ionic currents and lead to shortening action potential duration, increased automaticity, and trigger activity.<sup>25-27</sup> Shortening of the action potential and ERP has also been demonstrated in the ventricles.<sup>28-30</sup> However, other studies in human or dogs have provided conflicting results on the effect of acute pressure or volume load on atrial refractoriness, attributed as the means of causing stretch or the degree of stretch.<sup>31,32</sup> The acute LA stretch with associated neurohumoral changes resulted in abbreviation of atrial ERP and may partially explain the increased inducibility of AF observed with ventricular infarction alone.

### Atrial Ischemia or Infarction

LA ischemia/infarction because of occlusion of proximal LCX artery resulted in profound slowing in conduction velocity with

increased areas of isochronal crowding and marked increased in heterogeneity in conduction, all established prerequisites for the development of reentry and AF.<sup>9</sup> Sinno et al<sup>9</sup> have previously observed similar findings when targeting isolated atrial branches. Although clinically isolated atrial branch occlusion is rare, the findings of this study, mimicking the clinical scenario, confirm the importance of atrial ischemia in the development of the AF substrate. AF after MI tends to recur in >22% of the cases during late follow-up.<sup>1,6</sup> Although LV dysfunction is strongly associated with development of AF recurrence after MI,<sup>6</sup> some studies have shown AF recurrence post-MI was independent of LV dysfunction.<sup>1</sup> Furthermore, patients post-MI with atrial structural abnormalities, such as enlarged LA, have increased propensity for AF recurrence. In a canine model of chronic (>7 days) coronary artery occlusion, Nishida et al<sup>33</sup> found that stable reentrant sources at the border of atria infarcted area was associated with significant peri-infarct fibrosis. Atrial fibrosis is likely an important factor in stabilizing reentry and promoting AF. Acute atrial ischemia together with LA stretch synergistically interacts resulting in significant slowing in conduction velocity and marked increase in conduction heterogeneity as observed in LCX group. These electrophysiological changes are consistent with previous observations at the ventricular level.<sup>34,35</sup> In addition, the significant reduction in atrial ERP observed with acute MI is consistent with observations by Jayachandran et al.<sup>36</sup> However, the reduction in ERP in this study was equivalent and persistent in both LCX and LAD group suggesting that it was more likely because of LA stretch and the associated hemodynamic and neurohumoral changes associated with MI rather than because of atrial ischemia per se.

### Mechanisms of Ischemia Related Atrial Changes

The major pathophysiological conditions resulting from acute MI are elevated extracellular potassium, acidosis, and anoxia. These changes lead to reduction in membrane excitability, shortening of action potential duration, and prolongation of recovery of excitability after an action potential.<sup>37,38</sup> It is difficult to determine the ionic mechanisms of the electric changes and the contribution of each pathophysiological condition to each electric change. However, using an ionic-based theoretical model of cardiac ventricular cells exposed to the above pathological conditions (elevated  $[K]_o$ , acidosis and anoxia), Shaw et al<sup>38</sup> found that the depression of membrane excitability and delayed recovery of excitability caused by elevated  $[K]_o$  with additional excitability depression by acidosis. In addition, the major changes in action potential duration (shortening) can only be explained by anoxia-dependent opening of  $I_{K(ATP)}$ .

### Clinical Implication

Atrial ischemia or infarction with increased LA pressure plays an important role in LA electric changes that promotes AF occurrence during the acute phase of MI. It is likely that such changes may be responsible for the late and significant recurrences of AF after MI. Recent clinical data has suggested the importance of atrial branch compromise in patients with coronary artery disease as an important determinant of



developing AF.<sup>14</sup> Given the paroxysmal nature of AF after MI with usage of dual antiplatelet therapy in patients with coronary stenting, oral anticoagulation has been underused in this population.

The drug efficacy in treating AF may be related to the underlying mechanisms.<sup>39</sup> In experimental models, class III antiarrhythmic drugs are more effective in AF associated with structural remodeling than in atria remodeled by sustained atrial tachycardia. Likewise  $\beta$ -blockade and calcium channel blockers inhibit the arrhythmogenic consequences of acute atrial ischemia, whereas Na<sup>+</sup> channel or K<sup>+</sup>-channel blockers are ineffective.<sup>40</sup> In addition, other studies have also shown the favorable effect of early coronary reperfusion on AF incidence post-MI which may, in part, be explained by reduced total ischemic burden at both the ventricular and atrial level.<sup>14,41</sup> Atrial ischemia or infarction is rarely considered as a direct contributor to the development of AF after AMI. This study showed the direct relation between AF and atrial infarction. Moreover, the efficacy of different antiarrhythmic drugs may be related to the underlying substrate with the potential therapeutic implications of AF mechanisms related to acute atrial infarction.

### Study Limitations

This study evaluated the changes in the atrial electric changes during the initial 45 minutes of MI. The impact of neurohumoral factors has not been fully evaluated in this study. Finally, this is an ovine model with MI induced by balloon inflation in the coronary arteries; the pathogenesis of MI in humans is the result of plaque rupture and thrombosis, which might imply a different cardiovascular response.

### Conclusions

The pathophysiology of AF after MI is multifactorial, but atrial ischemia has dominant role in the development of the substrate for AF.

### Disclosures

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### CLINICAL PERSPECTIVE

Atrial infarction (AF) or ischemia is an important contributor to the development of AF after myocardial infarction. Coronary artery disease involving the atrial circulation (sinoatrial branch or left circumflex branches) carries the risk of atrial infarction with the creation of substrate for AF development and recurrence. Early coronary perfusion may reduce the risk of AF development after AMI.