Myocardial Infarction and Atrial Fibrillation: Importance of Atrial Ischemia

Running title: Alasady et al. AF in myocardial infarction

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Abstract

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

**Method and Results** - Forty-four sheep were studied. MI was induced by occlusion of the 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 over 45 minutes to determine: atrial effective refractory periods (ERP); conduction velocity (CV); conduction heterogeneity index (CHI); and AF inducibility. Post-mortem evaluation was performed with TTC staining.

MI resulted in greater LV dysfunction (P<0.05), LA pressure (p<0.0003) and reduction in atrial ERP (P<0.0001) compared to control. TTC staining demonstrated that the LCX and not the LAD group had atrial infarction. The LCX group demonstrated the following compared to the LAD or control groups: greater slowing in atrial CV (P<0.0001 and P<0.001); increased absolute range of conduction phase delay (P<0.001 and P<0.001); increased CHI (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 CV (P<0.01) but no change in CHI or AF duration compared to control.

**Conclusions** - Left ventricular infarction, which is known to result in atrial stretch, hemodynamic change and neurohumeral activation, contributes partially to the atrial abnormalities in MI. Atrial ischemia/infarction results in greater atrial electrical changes and propensity for AF; forming the dominant substrate for AF in MI.

**Key words**: atrial fibrillation, remodeling, myocardial infarction, myocardial ischemia, acute coronary syndrome
Introduction

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

The role for atrial ischemia/infarction in the pathogenesis of AF after MI has been suggested.\(^9\) Atrial infarction has been observed in 17% of MI patients in a large post-mortem study.\(^10\) In addition, an increased risk of atrial tachyarrhythmia has been observed in patients with atrial infarction.\(^11\),\(^12\) In a post-mortem series, James et al 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 sino-atrial branch which arises from the right coronary artery in 50-60% of the cases or the left circumflex artery in 40-50% of the cases.\(^13\) 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.\(^12\),\(^14\)\(^-\)\(^16\)

In sheep, the circumflex coronary artery (LCX) is the dominant coronary arterial supply to the atria. In contrast, while the left anterior descending (LAD) supplies an equivalent extent of the ventricular myocardium it does not have a major contribution to the atria.\(^17\) This anatomic difference in blood supply provides a unique model to evaluate the role of atrial ischemia/infarction. In the current 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 perpetuators such as
atrial stretch, haemodynamic change and neurohumural activation.

Methods
Forty-four Merino-Cross Wethers with a weight of 56±8 kg were studied (Figure-1). Following
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 anaesthesia. Sodium thiopental (15-20mg/kg) was
used for induction to facilitate endotracheal intubation and isoflurane (2-4%) in 100% oxygen
was used for maintenance. Invasive blood pressure, heart rate, LA pressure (LAP), end-tidal
CO₂, 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 Scientific,USA) 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 three
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 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 following balloon inflation. The presence of infarction was identified by staining with TTC (2,3,5Triphenyl tetrazolium chloride).18-20

Electrophysiology study

Open chest electrophysiological studies were performed. Using a limited pericardiotomy, a custom designed 64-electrode plaque with 5mm inter-electrode 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,USA). Electrograms were filtered from 30-500Hz, and measured with computer-assisted callipers at a sweep speed of 200mm/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 ERP was measured by pacing from one pre-specified corner of the plaque at twice diastolic threshold at cycle lengths(CL) of 400 and 250ms. A single extrastimulus(S2) was introduced after 8 basic stimuli(S1) starting with a coupling interval of 300ms and reducing in 10ms 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 three-times at each CL at each time point, and if the maximum and minimum differed by>10 ms, two additional measurements were taken and the total averaged.
Atrial conduction

Conduction was assessed during stable S1-pacing at 400 and 250ms. Activation maps were created using semi-automated custom made software.21,22 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.21,22 A mean conduction velocity can then be derived.

Conduction heterogeneity was assessed using phase mapping techniques during S1-pacing.23 In brief, the largest activation time difference between every four adjacent electrodes was first determined and divided by inter-electrode 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 (CHI) was calculated by dividing the absolute phase delay by the median (P50). The CHI is used to evaluate the heterogeneity in conduction in the atrial tissue.

AF vulnerability

The inducibility and duration of AF was evaluated using extra stimuli program 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 ≥2s. 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 was collected.

Statistical analysis

Data analysis were performed using SAS version 9.2 (SAS Institute Inc., Gary,NC,USA). All continuous variables are reported as mean±SD and assessed for normality utilizing the Shapiro-
Wilk test. The changes in haemodynamic were assessed using an ANOVA. To compare changes in the outcome measures between the three treatments 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 while animal was fitted as a random effect. The changes in the electrical 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. Due to high variation or over-dispersion 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, TTC staining demonstrated that the LCX and not the LAD group or the controls had atrial infarction (LCX 11 vs. LAD 0; P<0.05 and LCX 11 vs 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 (MAP) over time. The LVEF was similar between the groups at baseline (LCX vs. LAD vs. control: 60±4 vs. 61±3 vs. 62±5%, p=ns). There was a significant reduction in LVEF in the two MI groups 30 minutes post balloon inflation compared to control (LAD 37±2.7% [P=0.0002]; and LCX 36± 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 to 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 to control at 30-minutes post balloon inflation (LCX vs. control [p= 0.02]; LAD vs. control [p=0.03]). There was no significant difference in heart rate between LCX and LAD over time (P=0.5).

**Atrial electrical changes due to MI**

*Effective Refractory Period*

The left atrial ERP shortened in both MI groups compared to 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 while 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). Left ventricular infarction alone, as observed in the LAD group, induced a modest but significant change in conduction compared to control (P=0.01). However, with additional atrial ischemia as observed in the LCX group, there was marked and progressive slowing of conduction compared to 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 CHI (to express the heterogeneity of conduction, overall mean P5-95/P50) (Figures-6). The absolute range of conduction phase delay was increased in the LCX group compared to LAD (P<0.001) or control (P<0.001; Figure 6A). The CHI was markedly increased in the LCX group compared to 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 to LAD (LCX vs. LAD, IRR 6 [2-18], P=0.001) or control group (LCX vs. 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 LAD or control groups (p<0.05; Figure-7B). Three (27%) in LCX groups developed sustained AF while 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 (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 left ventricular function or the haemodynamic changes that occur during the
acute phase of MI. As a result of these abnormalities, not only was AF more frequently induced but 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,\textsuperscript{2-4,7,8,24} data on AF pathophysiogy after MI is limited.\textsuperscript{9} To our knowledge, no prior study has evaluated the relative influence of factors associated with acute MI that contribute to the AF substrate.

**Ventricular Infarction, atrial stretch and the haemodynamic 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 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.\textsuperscript{25-27} Shortening of the action potential and/or ERP has also been demonstrated in the ventricles.\textsuperscript{28-30} 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.\textsuperscript{31,32} The acute LA stretch with associated neurohumural 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 due to 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 pre-requisites for the development of re-entry and AF. Sinno et al have previously observed similar findings when targeting isolated atrial branches. While clinically isolated atrial branch occlusion is rare, the findings of the current 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 more than 22% of the cases during late follow up. While left ventricular dysfunction is strongly associated with development of AF recurrence after MI, some studies have shown AF recurrence post MI was independent of LV dysfunction. 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 K et al found that stable re-entrant sources at the border of atria infarcted area was associated with significant peri-infarct fibrosis. Atrial fibrosis is likely an important factor in stabilizing re-entry 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. In addition, the significant reduction in atrial ERP observed with AMI is consistent with observations by Jayachandran et al. However, the reduction in ERP in the current study was equivalent and persistent in both LCX and LAD group suggesting that it was
more likely due to LA stretch and the associated hemodynamic and neurohumural changes associated with MI rather than due to 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 (APD) and prolongation of recovery of excitability following an action potential.\textsuperscript{37,38} It is difficult to determine the ionic mechanisms of the electrical changes, and the contribution of each pathophysiological condition to each electrical change. However, using an ionic-based theoretical model of cardiac ventricular cells exposed to the above pathological conditions (elevated $[K]\textsubscript{o}$, acidosis and anoxia), Shaw et al found that the depression of membrane excitability and delayed recovery of excitability caused by elevated $[K]\textsubscript{o}$ with additional excitability depression by acidosis.\textsuperscript{38} In addition, the major changes in action potential duration (shortening) can only be explained by anoxia-dependent opening of $I_{K(\text{ATP})}$.

Clinical Implication

Atrial ischemia or infarction with increased LA pressure plays an important role in LA electrical 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.\textsuperscript{14} Given the paroxysmal nature of AF after MI with usage of dual antiplatelet therapy in patients with coronary stenting, oral anticoagulation has been underutilised in this population.

The drug efficacy in treating AF may be related to the underlying mechanisms.\textsuperscript{39} In experimental models, class III antiarrhythmic- drugs are more effective in AF associated with structural remodelling than in atria remodelled by sustained atrial tachycardia. Likewise beta-
blockade and calcium channel blockers inhibit the arrhythmogenic consequences of acute atrial ischemia, whereas Na$^+$ channel or K$^+$-channel blockers are ineffective.\textsuperscript{40} In addition, other studies have also shown the favourable effect of early coronary reperfusion on AF incidence post MI which may in part be explained by reduced the total ischemic burden at both the ventricular and atrial level.\textsuperscript{14,41} 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 anti-arrhythmic drugs may be related to the underlying substrate with the potential therapeutic implications of AF mechanisms related to acute atrial infarction.

\textbf{Study limitations}

This study evaluated the changes in the atrial electrical changes during the initial 45 minutes of MI. The impact of neurohumoral factors have 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.

\textbf{Conclusion}

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

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\textbf{Conflict of Interest Disclosures:} KCRT reports having served on the advisory board of St Jude Medical. PS reports having served on the advisory board of Medtronic, St Jude Medical, Sanofi-Aventis and Merck. PS reports having received lecture fees and research funding from Biosense-Webster, Medtronic, Boston Scientific, Biotronik and St Jude Medical.
References:


**Figure Legends:**

**Figure 1:** (A) Summary of the study design (LAD=left anterior descending artery, LCX=left circumflex artery and CTL=control). (B) Infarcted tissue (red arrow) in left anterior descending artery territory (LAD) highlighted using TTC staining.

**Figure 2:** (A) Hemodynamic changes of the three 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 three groups (LCX, LAD and control). It shows a significant increase in LAP in MI group compared to control. Meanwhile, there was no difference in LAP between LCX and LAD.

**Figure 3:** Changes in atrial ERP at cycle length 400 msc over 45 minutes after balloon inflation. There was a significant reduction ERP over time which started as early as 30 minutes and persisted in MI groups (LCX and LAD) compared to control (P=004). There was no significant difference between LCX and LAD groups.
Figure 4: Representative activation maps from each group at 15 minutely intervals for the study duration at a CL 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, isochronal crowding with susceptibility to reentry.

Figure 5: Conduction velocity with time in each of the groups. Demonstrated is the marked and progressive slowing in CV in LCX group compared to LAD or control. There was modest reduction in CV in LAD group compared to controls.

Figure 6: (A) Absolute inhomogeneity of conduction (P5-95). The LCX group demonstrates marked and progressive changes compared to LAD or control. This was evident 15 minutes after angioplasty balloon inflation in LCX. (B) Conduction heterogeneity index (CHI) significantly increased over 45 minutes (15 minutely intervals) in LCX group compared to LAD or control. The result was evident 30 minutes post MI.

Figure 7: (A) Number of AF episodes in each group during ERP testing. This was significantly higher in LCX groups compared to 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.
44 Sheep

11 Controls

22 MI

11 excluded due to premature death

11 LCX (LA ischemia)

11 LAD (no LA ischemia)
Infarcted tissue of the Left ventricular (white colour)
B

Mean Duration of AF

Duration (seconds)

Group

Control
LAD
LCX

Error bars: 95% CI
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