Effects of Iatrogenic Myocardial Injury on Coronary Microvascular
Function in Patients Undergoing Radiofrequency Catheter
Ablation of Atrial Fibrillation

Running title: Lim et al.; Microvascular dysfunction after catheter ablation

Hong Euy Lim, MD; Cheol Ung Choi, MD; Jin Oh Na, MD; Jong-Ill Choi, MD;
Seong Hwan Kim, MD; Jin Won Kim, MD; Eung Ju Kim, MD; Seoung Woo Han, MD;
Sang Weon Park, MD; Seung-Woon Rha, MD; Chang Gyu Park, MD; Hong Seog Seo, MD;
Dong Joo Oh, MD; Chun Hwang, MD; Young-Hoon Kim, MD

1Cardiovascular Center, Division of Cardiology, Department of Internal Medicine, Korea
University Guro Hospital, Korea University College of Medicine, Seoul; 2Division of Cardiology,
Department of Internal Medicine, Korea University Ansan Hospital, Gyeonggi-Do, Republic of
Korea, 3Division of Cardiology, Utah Valley Regional Medical Center, Provo, UT

Corresponding Author:
Cheol Ung Choi, MD, PhD
Cardiovascular Center, Division of Cardiology
Department of Internal Medicine
Korea University Guro Hospital
Korea University College of Medicine
97, Guro-dong, Guro-gu
Seoul 152-703, Korea
Tel: +82 2 2626 3025
Fax: +82 2 863 1109
E-mail: wmagpie@korea.ac.kr / wmagpie@korea.com

Journal Subject Codes: [5] Arrhythmias, clinical electrophysiology, drugs
Abstract

**Background** - Iatrogenic myocardial injury by radiofrequency catheter ablation (RFCA) releases pro-inflammatory substances from damaged myocardium, and these may contribute to endothelial dysfunction in systemic vascular structure. The aim of this study is to evaluate effect of non-ischemic myocardial damage on coronary microvascular function in patients undergoing atrial fibrillation (AF) ablation.

**Methods and Results** - We included 49 patients who underwent AF ablation (paroxysmal AF[PAF] = 25, persistent AF[PeAF] = 24) and 34 controls. Immediately before and after RFCA, index of microvascular resistance (IMR) was assessed at left anterior descending coronary artery and blood samples were obtained for analyses of nitric oxide (NO), activated leukocyte cell adhesion molecule (ALCAM), and lipoprotein-associated phospholipase (LpPLA2). Transthoracic echocardiography was performed at baseline, one day, one month, and 3 months after RFCA. Compared with baseline, IMR, ALCAM, and LpPLA2 increased and NO decreased after RFCA. In 36 subjects with increasing IMR, E/E’ ratio increased at one day and returned to baseline level at 3 months after RFCA. Changes in ALCAM and LpPLA2 between baseline and after RFCA were independently related to the increase in IMR. In 14 subjects (28.6%), arrhythmia recurred. Using a cutoff value of 9.3 mmHg/s, sensitivity was 56.7% and specificity was 91.2% for IMR change in predicting AF recurrence (P = 0.028).

**Conclusions** - Myocardial damage by RFCA provoked coronary microvascular dysfunction through systemic pro-inflammatory reaction that may contribute to transient diastolic dysfunction. This phenomenon may represent a mechanism for early recurrence of arrhythmia following RFCA.

**Clinical Trial Registration Information** – [http://cris.cdc.go.kr](http://cris.cdc.go.kr); Identifier: KCT0000030.

**Key words:** atrial fibrillation, catheter ablation, coronary microvascular function, Index of microvascular resistance
Introduction

Radiofrequency catheter ablation (RFCA) has emerged as an effective and curative treatment option for atrial fibrillation (AF) and its use is increasing exponentially.\(^1\) However, substantial number of patients experience arrhythmia recurrence, especially during a transient time after AF ablation defined as “the blanking period”.\(^2\)\(^-\)\(^5\) Several hypotheses may potentially explain this early recurrence, including local and/or systemic inflammation,\(^3\)\(^-\)\(^4\) however, the mechanism for early recurrence has not been fully elucidated.

Iatrogenic myocardial damage induced by RFCA releases pro-inflammatory substances into systemic circulation from the damaged myocardium\(^6\)\(^-\)\(^7\) and these provoke the perturbation of endothelial function in the coronary microvasculature.\(^8\) This endothelial dysfunction may potentially induce diastolic dysfunction of the left ventricle (LV) and thereby contribute to early recurrence of arrhythmia after AF ablation. However, there was no data relating non-ischemic myocardial damage to coronary microvascular function and LV diastolic function.

In the present study we aimed to determine whether iatrogenic myocardial injury provokes coronary microvascular dysfunction and LV diastolic dysfunction, and whether this consequence influences early recurrence of AF after RFCA. We registered this prospective study as KCT0000030 at Clinical Research Information Service, Korea Centers for Disease Control and Prevention (http://cris.cdc.go.kr).

Methods

Study Population

From September 2010 to September 2011, we consecutively enrolled 136 patients who underwent RFCA for paroxysmal AF (PAF, \(n = 73\)) and persistent AF (PeAF, \(n = 63\)). The control group consisted of 34 patients undergoing RFCA for supraventricular tachycardia. PAF
or PeAF were defined according to the most recent guideline of the Heart Rhythm Society and European Cardiac Arrhythmia Society. Attempting to control for intrinsic limitations of beat-to-beat variations caused by AF, we included only subjects who had sinus rhythm (SR) for at least 24 hours prior to the examination. Then, subjects with AF at the time of enrollment were conducted direct current (DC) cardioversion and then monitored by continuous electrocardiography (ECG). Other exclusion criteria were significant coronary artery disease (more than 50% fixed stenosis), the presence of visible thrombi in left atrium (LA) by transesophageal echocardiography (TEE), previous AF ablation or cardiac surgery, aortic aneurysm or dissection, cardiomyopathy, more than mild valvular disease, congenital heart disease, an acute cerebrovascular event within the preceding 3 months, any major trauma or surgery within the preceding 3 months, hyperthyroidism, uncontrolled hypertension, malignancy, connective tissue disease, and any acute or chronic inflammatory diseases. All anti-arrhythmic drugs were discontinued at least five half-lives prior to the examination. Amiodarone was discontinued at least 8 weeks earlier. All patients were on continuous anticoagulation therapy with a target international normalized ratio of 2 to 3. Each participant signed an informed consent form prior to the study, which was approved by the Human Subjects Review Committee of Korea University Hospital.

**Study Design**

In all subjects enrolled, a two-dimensional (2-D) transthoracic echocardiography (TTE) with Doppler study was conducted just before and at one day, one month, and 3 months after RFCA. In all AF patients, we measured the index of microvascular resistance (IMR), which is a well-known index for specific and quantitative assessment of coronary microcirculatory resistance to assess coronary microvascular function. Immediately before and after RFCA, the IMR was
measured and blood samples were obtained from the coronary sinus for analyses of high 
sensitivity C-reactive protein (hs-CRP), nitric oxide (NO), activated leukocyte cell adhesion 
molecule (ALCAM), and lipoprotein-associated phospholipase (LpPLA2) levels. From the 
peripheral venous blood, we analyzed B-type natriuretic peptide (BNP) level at baseline and at 
one day following RFCA. Cardiac enzymes including cardiac-troponin T, creatine kinase-MB 
(CK-MB), and myoglobin were also measured at one day following RFCA.

**Transthoracic Echocardiography**

All examinations were performed using a commercially available Vivid 7™ (GE Medical 
System, Vingmed, Horten, Norway) ultrasound system. All recorded echocardiograms were 
collected and analyzed using an off-line computer analysis station (Echopac™ 6.3.4; GE 
Medical Systems).

All measurements were taken from three consecutive cardiac cycles and averaged. The 
maximal LA volume (LAV) was manually measured using the modified Simpson’s method after 
zooming in on the LA by tracing the endocardial border in the apical four- and two-chambers 
over the cardiac cycle. Each echocardiographic parameter was determined according to the 
recommendations of the American Society of Echocardiography.12 Transmtral pulsed-wave 
Doppler velocities were recorded from the apical four-chamber view with a 2-mm Doppler 
sample placed between tips of the mitral leaflets. Early (E) and late (A) wave velocities and the 
E/A ratio were assessed from the mitral inflow profile. Pulsed-wave tissue Doppler imaging was 
obtained from the apical four-chamber view. A 2-mm sample volume was placed at the septal 
and lateral mitral annulus. Systolic (S’), early diastolic (E’), and late diastolic (A’) velocities 
were measured and the E/E’ ratio was calculated.
Measurement of Index of Microcirculatory Resistance

All AF patients underwent routine coronary angiography (CAG) using the Judkins technique on digitalized CAG equipment (FD-10, Philips Healthcare, Best, The Netherlands). After CAG, a coronary pressure wire (Radi Medical Systems, Uppsala, Sweden) was calibrated outside the body, equalized to the guiding catheter pressure with the sensor positioned at the ostium of the guiding catheter, and then advanced to distal of the left anterior descending (LAD) coronary artery. The IMR is defined as the distal coronary pressure divided by the inverse of the simultaneously measured thermodilution-derived hyperemic mean transit time (hTmn), or more simply, distal coronary pressure multiplied by the hTmn (mmHg/s or units [U]).

The mean transit time was measured at rest and during hyperemia by methods described previously. Briefly, with commercially available software (Radi Medical Systems), the shaft of the pressure wire can act as a proximal thermistor by detecting changes in temperature-dependent electrical resistance. The sensor near the tip of the wire simultaneously measures pressure and temperature and can thereby act as a distal thermistor. The transit time of room temperature saline injected down a coronary artery can be determined using a thermodilution technique.

Three injections of saline (3 ml, room temperature) were administered to the coronary artery and the baseline mean transit time (bTmn) was measured. Intravenous adenosine (140 mg/kg/min) was then administered to induce steady-state maximal hyperemia; three more injections of saline (3 ml, room temperature) were given, and the hTmn was measured. Simultaneous measurements of mean distal coronary pressure (Pd, by pressure wire) were also made in the resting and maximal hyperemic states.
Blood Sampling and Analysis

In all subjects, a blood sample was obtained from the coronary sinus just before and after RFCA for analysis of NO, ALCAM, LpPLA2 and hs-CRP levels. These values were used as indices for endothelial function and inflammatory substances. Blood samples were drawn into ice-chilled tubes containing ethylene diaminetetra-acetic acid and were immediately centrifuged at 3,000 rpm for 20 minutes. All samples were frozen at -80°C until assay. The samples were batched together for assay and processed by a technician blinded to all subject information.

NO was measured using a colorimetric NO assay kit (Oxford Biomedical Research) and data were expressed in micromoles per liter (μmol/l). Plasma ALCAM was quantified by an enzyme-linked immunoassay (ELISA) performed in duplicate samples using commercially available matched antibodies (R&D Systems, Minneapolis, MN, USA) and data were expressed as nanograms per milliliter (ng/ml). LpPLA2 was measured in plasma aliquots using an ELISA (PLAC test; diaDexus Inc., San Francisco, CA, USA); data were expressed in ng/ml. An ELISA (Alpha Diagnostic International, San Antonio, TX, USA) was used to measure hs-CRP in milligrams per liter (mg/l).

Blood samples were also obtained from a peripheral vein at one day after RFCA for analyses of cardiac-troponin T, CK-MB, myoglobin, and BNP levels. Cardiac-troponin T, CK-MB, myoglobin, and BNP were analyzed on a Stratus CS analyzer (Dade Behring, Germany), using commercially available test materials.

Ablation Procedure

Prior to RFCA, TEE and multi-slice computerized tomography (MSCT) were performed in all subjects. Intracardiac ECG was recorded using a PruckaCardioLab™ electrophysiology system (General Electric Health Care System, Inc., Milwaukee, WI, USA) and a 3-D electroanatomical
mapping system (NavX; St. Jude Medical Inc., Minnetonka, MN, USA) was used in all subjects.

After double transseptal puncture, systemic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time between 300 and 350 seconds. After the 3-D geometry of LA and pulmonary veins (PVs) was determined using the NavX mapping system and then merged with volume-rendered MSCT imaging, all PVs were mapped with a decapolar circular catheter (Lasso; Biosense Webster, Diamond Bar, CA, USA). An open-irrigation, 3.5-mm tip-deflectable catheter (Celsius; BiosenseWebster) was used for mapping and ablation. Radiofrequency energy was delivered at a maximum power output of 25-30 W, a flow rate of 17-30 ml/min, and a maximum temperature of 48°C. The end point for each individual application at a given site was either total voltage abatement or current application of up to 40 seconds with adequate tissue contact and power delivery. A stepwise ablation procedure was employed in all AF patients, regardless of AF type. Initially, all patients underwent wide circumferential PV isolation (CPVI). For patients who remained in SR after CPVI, an inducibility test with 10 mA pacing was performed in the high right atrium or coronary sinus using a pacing cycle length of 180 ms with a 1:1 capture. If induced AF was sustained for more than 10 minutes without isoproterenol infusion or patients who remained in AF after CPVI, an additional ablation of complex fractionated atrial electrogram (CFAEs) sites on both atria was completed until the termination of AF was observed. A CFAE was defined as an electrogram with a fractionated interval between 50 ms and 120 ms, displayed by color map on the NavX geometry. In cases where AF converted to organized atrial flutter (AFL), a local activation time map was created during stable AFL, and was displayed on the NavX geometry. Several rounds of radiofrequency energy were then delivered to the critical isthmus or foci until AFL termination was observed. In patients with PeAF and/or induced typical AFL, a cavotricuspid
Isthmus line was created and the bidirectional block was confirmed by a differential pacing maneuver. If subjects remained in AF up to 5 hours after beginning RFCA, we performed DC cardioversion to restore SR. Before the end of procedure, all ablated PVs were revisited and then PVS with evidence of reconnection were re-isolated.

Follow-up

If no complications arose during the procedure, anticoagulation therapy with warfarin was initiated without any antiarrhythmic medications. All subjects were prospectively followed for AF recurrence after RFCA at monthly outpatient clinic visits. Subjects also underwent 48-hour Holter monitoring at 1 and 3 months post-RFCA. An ECG was performed during every visit and at any time that the subject reported palpitations. Additionally, a nurse practitioner questioned each subject by telephone at 2-week intervals and all subjects were instructed to call whenever they experienced symptoms. Any patient with documented AF or AFL during the follow-up period was diagnosed as having a clinical arrhythmia recurrence and was treated with antiarrhythmic medications.

Statistical Analysis

All continuous variables were expressed as either the mean ± standard deviation or median (25th, 75th percentiles range), depending on the distribution. For continuous data, statistical differences were evaluated using Student's t-test or the Mann-Whitney U-test, depending on the data distribution. The paired t-test or Wilcoxon’s sign-ranked test were used for analyzing the changes of parameters between just before and after RFCA, depending on the data distribution. Nonparametric tests were used in analyzing hs-CRP, BNP and TG since they had not normal distribution. Categorical variables were presented as frequencies (percent) and were analyzed using the Fisher's Exact Test. Changes in the E/E' ratio from baseline at one day, 1 month, and 3
months after RFCA were analyzed using two-way repeated measures analysis.

To determine whether any of the variables were independently related to increasing IMR, multivariate logistic regression analysis of variables with a $P$-value of $<0.10$ in univariate analysis were performed. The area under the receiver-operating-characteristic (ROC) curve (AUC) was used to evaluate the discrimination of prediction of recurrence, and then to derive sensitivity and specificity values for each cutoff value. All statistical analyses were conducted using SPSS statistical software, version 13.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was set at $P \leq 0.05$ in two-sided tests.

**Results**

**Baseline Characteristics**

Of the 136 patients with AF initially enrolled, 58 who had AF within 24 hours prior to the examination, 24 who presented significant coronary artery stenosis during CAG, and 5 in whom attempts to advance the pressure wire to distal of LAD coronary artery failed, were excluded from this analysis. The final study group then included 49 subjects with AF (PAF, $n = 25$ and PeAF, $n = 24$) and 34 controls. All AF subjects were followed until the end of the study period (3 months following RFCA). AF recurred in one (PeAF = 1) patient at one day, 9 (PAF = 2, PeAF = 7) patients during the first month, and 4 (PAF = 1, PeAF = 3) patients during 3 months after RFCA. There were no procedure related complications in all subjects. The baseline demographic and echocardiographic parameters of study participants are summarized in Table 1. Male was more common and LA size was larger in AF subjects compared with controls. Of AF patients, the IMR was increased after RFCA in 36 subjects and there were no significant differences in baseline characteristics between two groups.

Changes of biomarker levels and IMR before and after RFCA are summarized in Table 2.
Compared with controls, pre-BNP, pre- and post-RFCA ALCAM, and post-RFCA hs-CRP and BNP were much higher in AF subjects. Changes of hs-CRP, NO, ALCAM, and LpPLA2 between just before and after RFCA were significantly greater in AF group. However, there were no significant differences between PAF and PeAF. Compared with subjects who did not have increasing IMR (n=13), post-RFCA NO was significantly lower and post-RFCA ALCAM was significantly higher in subjects with increasing IMR. Changes of ALCAM and LpPLA2 between just before and after RFCA were significantly greater in subjects with increasing IMR. However, there was no statistical difference in pre- and post-RFCA BNP level in AF subjects. The cumulative energy application (e.g. ablation time and cardiac enzymes after RFCA) was not different between the two groups.

**Changes of IMR, NO, ALCAM, and LpPLA2**

Figure 1 and 2 show changes in IMR, NO, ALCAM, and LpPLA2 in AF patients and controls. In AF subjects with early recurrence, IMR (16.6 ± 10.5 mmHg/s vs. 26.9 ± 13.3 mmHg/s, P < 0.001, Figure 1B), ALCAM (2.21 ± 1.20 ng/ml vs. 2.77 ± 0.92 ng/ml, P = 0.016), and LpPLA2 (268.2 ± 79.9 ng/ml vs. 309.6 ± 77.7 ng/ml, P = 0.001) were significantly increased after RFCA compared those before RFCA (Figure 2). NO was significantly decreased after RFCA in all AF subjects, irrespective of early recurrence (Figure 2-A). However, there were no significant differences in levels of NO, ALCAM, and LpPLA2 in control group between before and after RFCA (Figure 2).

**Changes in the E/E’ Ratio**

Figure 3 illustrates changes in the E/E’ ratio from baseline to values at one day, one month and 3 months after RFCA. In subjects with increasing IMR, the E/E’ ratio was significantly increased at one day after RFCA, decreased at one month, and returned to the baseline level at 3 months.
following RFCA. However, in subjects without increasing IMR, the E/E’ did not change significantly.

**Parameters for Increasing IMR in Logistic Regression Analysis**

Table 3 shows the logistic regression analysis for variables related to an increase in IMR after RFCA for AF. Changes in ALCAM and LpPLA2 between just before and after RFCA were independently related to increasing IMR after adjustment for LAV, the E-wave, and the serum myoglobin.

**Predictors for Early Recurrence in Logistic Regression Analysis**

Table 4 showed that PeAF, LAV, myoglobin, ablation time, total procedure time, and the change in IMR were independently predictors for early recurrence following AF ablation.

**The Change in IMR for Prediction of Early Recurrence after AF Ablation**

Figure 4 shows the ROC curve of the IMR change for prediction of early recurrence following RFCA for AF. Using a cutoff value of 9.3 mmHg/s in IMR change, the sensitivity was 46.7% (95% confidence interval = 0.248-0.699) and specificity was 91.2% (95% confidence interval = 0.770-0.970).

**Discussion**

The noteworthy findings of the present study are as follows: 1) non-ischemic, iatrogenic myocardial injury through RFCA provoked coronary microvascular dysfunction, which may be caused by pro-inflammatory substances (ALCAM, LpPLA2) released from damaged myocardial endothelium into systemic circulation; 2) LV diastolic dysfunction, assessed from the E/E’ ratio and possibly attributable to increased IMR, was reversible within 3 months after RFCA; 3)
Increasing IMR as well as PeAF and LAV was independently associated with arrhythmia recurrence in the first 3 months following RFCA for AF; and 4) the increase in IMR of >9.3 mmHg/s may present a new parameter for identifying patients at high risk for early recurrence after AF ablation.

Although RFCA has been considered as an effective and curative treatment option for AF, early recurrence within 1-3 months following AF ablation is reported to occur in 35% to 65% of patients treated with RFCA.\textsuperscript{15-17} Although arrhythmia recurrence during this early period is regarded as a prominent factor in long-term AF recurrence, approximately 50% of the patients who have early recurrence remain free from AF in the absence of any further treatments including antiarrhythmic drugs during the long-term follow-up.\textsuperscript{15} Therefore, both clinical trial results and the experience of many investigators indicate that early recurrence does not necessarily represent procedural failure. This transient increase in risk may hypothetically be explained as a “the blanking period,” following RFCA. Several mechanisms likely account for the heightened vulnerability during the blanking period include local inflammation in the damaged myocardium, heightened adrenergic tone, and changes in medications and in fluid and electrolyte balance.\textsuperscript{2, 4, 5}

We found that in a substantial number of patients, LV diastolic function decreased initially but recovered within 3 months following RFCA (Figure 3). This transient LV diastolic dysfunction was only observed in patients with increasing IMR. This result might indicate that impairment of myocardial blood supply caused by coronary microvascular dysfunction makes an important contribution to LV diastolic dysfunction. Furthermore, since LV diastolic dysfunction plays a prominent role in creating an arrhythmogenic substrate,\textsuperscript{18, 19} our original findings present a plausible mechanism for early recurrence during the blanking period.
Several substances related to endothelial dysfunction and inflammatory response are released into systemic circulation. NO, produced by endothelial cells, maintains the endothelium in a constant state of vasodilatation and may act to attenuate pro-inflammatory response and inhibit adhesion molecule expression. Circulating adhesion molecules reflect an inflammatory interaction between endothelial cells and leukocytes, and are strongly associated with the adverse outcome among patients with coronary artery disease, acute coronary syndromes, and heart failure. In addition, circulating adhesion molecules contribute to microvascular dysfunction as inflammatory mediators. Through binding to the capillary lumen, ALCAM facilitate migration of leucocytes through capillary walls into surrounding tissues. Resulting cellular and intracellular edema may lead to blood vessel congestion and impaired coronary perfusion. LpPLA2 circulates in association with low density lipoprotein and promotes vascular inflammation through hydrolysis of sn-2 fatty acids of oxidized phospholipids to oxidized fatty acid and lysophosphadidylincholine. These particles amplify the inflammatory response and may further increase LpPLA2 levels.

We demonstrated that changes in ALCAM and LpPLA2 between baseline and after RFCA for AF were independently associated with increasing IMR (Table 3) and the increase in IMR between just before and after RFCA was independent predictor for early recurrence following AF ablation (Table 4). These findings suggest that circulating pro-inflammatory substances released from damaged myocardial cells contributed to the coronary microvascular dysfunction, resulted in arrhythmia recurrence during the blanking period. However, we observed increasing IMR in only about 3/4 patients who underwent AF ablation. In addition, increase in ALCAM and LpPLA2 following RFCA was only observed in AF patients with early recurrence, whereas there were no significant changes in patients without recurrence and controls.
(Figure 2). Furthermore, our study demonstrated that the amount of myocardial damage, which represented with ablation time, CK-MB, troponin-T, and myoglobin, was not independently related to early recurrence following RFCA for AF (Table 4). These results suggest that profound activation of circulating adhesion molecules may be influenced by other factors rather than non-ischemic myocardial injury itself or catheter manipulation in the heart.

**Limitations**

First limitation in our study is the intentional selection of patients who had SR at the time of enrollment so as to minimize beat-to-beat variations from AF itself and potential effects of these variations on circulating inflammatory substances and coronary microvascular endothelial function. Since we may thereby have excluded patients with profound LA remodeling, our results may not be extrapolated to patients with long-lasting PeAF or permanent AF. Second, we measured BNP levels at baseline and after RFCA, and there were no significant differences in study populations, irrespective of AF type and the change in IMR. Since we used the irrigation ablation catheter in all AF patients, change of volume status for a short period time may influence BNP levels in our results. Therefore, we suggested that tissue Doppler study might be more appropriate modality to assess LV diastolic function in patient undergoing RFCA for AF.

Third, we proposed that, using a cutoff value of 9.3 mmHg/s, the increase in IMR may present an identifying marker for high risk patients who are likely to experience early recurrence during the blanking period after RFCA for AF. However, the clinical relevance may be limited, because the measurement of IMR is not always applicable in clinical practice. Fourth, sample size was relatively small. For the purpose of a greater clinical perspective, a large-scale, multicenter study should be needed. Finally, we could not provide serial assessments for IMR from coronary artery and pro-inflammatory biomarkers from coronary sinus during the follow-up period in AF.
patients as well as controls for ethical reasons. Therefore, we cannot conclude that the reversal of LV diastolic dysfunction is directly associated with improvement of coronary microvascular function and exactly distinguish between a direct and a by-stander role of pro-inflammatory substances in pathophysiology of early recurrence. Further investigations are indicated, using a simple, reproducible and non-invasive technique to assess coronary microvascular function.

Conclusions

We have shown for the first time that non-ischemic, iatrogenic myocardial damage induced by RFCA may evoke coronary microvascular endothelial dysfunction through increasing systemic levels of adhesion molecules; these pro-inflammatory substances may in turn contribute to transient LV diastolic dysfunction. This phenomenon may represent a potential mechanism for increased risk of early recurrence during the blanking period following AF ablation. We propose that measurement of coronary microvascular dysfunction may serve as a useful criterion to identify patients who are likely to experience early recurrence after AF ablation. Furthermore, pharmacologic inhibitors of adhesion molecule expression may potentially prevent early recurrence following RFCA for AF.

Conflict of Interest Disclosures: None.

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Table 1. Baseline Characteristics and Echocardiographic Measurements in Controls and AF Patients

<table>
<thead>
<tr>
<th></th>
<th>Control (n=34)</th>
<th>AF (n=49)</th>
<th>P Value</th>
<th>AF Not Increased IMR (n=13)</th>
<th>AF Increased IMR (n=36)</th>
<th>P Value</th>
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<tr>
<td>Age (yrs)</td>
<td>45 ± 19</td>
<td>52 ± 12</td>
<td>0.057</td>
<td>53 ± 11</td>
<td>52 ± 12</td>
<td>0.658</td>
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<td>Male (%)</td>
<td>18 (51.4)</td>
<td>40 (81.6)</td>
<td>0.004†</td>
<td>12 (92.3)</td>
<td>28 (77.8)</td>
<td>0.412†</td>
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<td>Body mass index (kg/m2)</td>
<td>23.39 ± 4.23</td>
<td>25.54 ± 2.88</td>
<td>0.334</td>
<td>25.39 ± 2.23</td>
<td>25.59 ± 3.10</td>
<td>0.700</td>
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<tr>
<td>HTN (%)</td>
<td>8 (22.9)</td>
<td>17 (34.7)</td>
<td>0.334†</td>
<td>6 (46.2)</td>
<td>11 (30.6)</td>
<td>0.331†</td>
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<td>DM (%)</td>
<td>2 (5.7)</td>
<td>4 (8.2)</td>
<td>1.000†</td>
<td>1 (7.7)</td>
<td>3 (8.3)</td>
<td>1.000†</td>
</tr>
<tr>
<td>PeAF (%)</td>
<td>24 (49.0)</td>
<td></td>
<td></td>
<td>6 (46.2)</td>
<td>18 (50.0)</td>
<td>1.000†</td>
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<tr>
<td>T-Chol (mg/dl)</td>
<td>188 ± 35</td>
<td>175 ± 35</td>
<td>0.115</td>
<td>163 ± 32</td>
<td>179 ± 35</td>
<td>0.108</td>
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<tr>
<td>Triglyceride (mg/dl)</td>
<td>103 (66.75, 157)</td>
<td>118 (88.50, 167)</td>
<td>0.203‡</td>
<td>117 (86, 130)</td>
<td>126 (88.25, 176.25)</td>
<td>0.497‡</td>
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<td>HDLC (mg/dl)</td>
<td>55 ± 14</td>
<td>49 ± 14</td>
<td>0.085</td>
<td>47 ± 13</td>
<td>50 ± 15</td>
<td>0.919</td>
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<td>LDLc (mg/dl)</td>
<td>104 ± 32</td>
<td>106 ± 29</td>
<td>0.854</td>
<td>98 ± 26</td>
<td>109 ± 29</td>
<td>0.213</td>
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<tr>
<td>LVIDd (mm)</td>
<td>47.61 ± 4.57</td>
<td>51.85 ± 4.77</td>
<td>0.002</td>
<td>53.13 ± 5.02</td>
<td>51.39 ± 4.67</td>
<td>0.519</td>
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<td>LVIDs (mm)</td>
<td>30.42 ± 4.76</td>
<td>33.47 ± 4.65</td>
<td>0.092</td>
<td>34.62 ± 5.08</td>
<td>33.06 ± 4.49</td>
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<td>LAD (mm)</td>
<td>35.91 ± 3.81</td>
<td>42.14 ± 7.38</td>
<td>0.015</td>
<td>41.44 ± 6.77</td>
<td>44.07 ± 8.86</td>
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<td>LVEF (%)</td>
<td>62.58 ± 0.80</td>
<td>63.57 ± 7.32</td>
<td>0.356</td>
<td>62.79 ± 6.78</td>
<td>63.85 ± 7.58</td>
<td>0.684</td>
</tr>
<tr>
<td>LAV (ml)</td>
<td>30.28 ± 14.40</td>
<td>72.04 ± 29.46</td>
<td>&lt;0.001</td>
<td>61.12 ± 22.32</td>
<td>81.20 ± 38.46</td>
<td>0.070</td>
</tr>
<tr>
<td>E-wave (cm/sec)</td>
<td>67.00 ± 19.87</td>
<td>76.76 ± 15.05</td>
<td>&lt;0.001</td>
<td>83.00 ± 12.48</td>
<td>74.50 ± 15.42</td>
<td>0.059</td>
</tr>
<tr>
<td>A-wave (cm/sec)</td>
<td>54.31 ± 15.62</td>
<td>64.96 ± 19.70</td>
<td>0.001</td>
<td>68.08 ± 23.03</td>
<td>63.83 ± 18.58</td>
<td>0.557</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.41 ± 0.80</td>
<td>1.29 ± 0.47</td>
<td>0.482</td>
<td>1.30 ± 0.35</td>
<td>1.28 ± 0.51</td>
<td>0.884</td>
</tr>
<tr>
<td>Deceleration time (msec)</td>
<td>199.10 ± 49.51</td>
<td>192.33 ± 88.98</td>
<td>0.704</td>
<td>228.18 ± 112.16</td>
<td>193.41 ± 47.44</td>
<td>0.298</td>
</tr>
<tr>
<td>E' wave (cm/sec)</td>
<td>8.44 ± 3.19</td>
<td>9.10 ± 2.28</td>
<td>0.210</td>
<td>8.87 ± 2.42</td>
<td>9.18 ± 2.26</td>
<td>0.697</td>
</tr>
<tr>
<td>A' wave (cm/sec)</td>
<td>8.17 ± 2.18</td>
<td>6.31 ± 2.60</td>
<td>0.002</td>
<td>7.52 ± 1.56</td>
<td>8.31 ± 2.55</td>
<td>0.201</td>
</tr>
<tr>
<td>E/E' ratio</td>
<td>9.08 ± 6.87</td>
<td>10.51 ± 3.93</td>
<td>0.220</td>
<td>9.95 ± 2.89</td>
<td>8.48 ± 2.15</td>
<td>0.113</td>
</tr>
<tr>
<td>Ablation time (min)</td>
<td>6 ± 3</td>
<td>112 ± 44</td>
<td>&lt;0.001</td>
<td>108 ± 30</td>
<td>114 ± 48</td>
<td>0.614</td>
</tr>
<tr>
<td>Total procedure time (min)</td>
<td>59 ± 33</td>
<td>144 ± 45</td>
<td>&lt;0.001</td>
<td>139 ± 30</td>
<td>146 ± 51</td>
<td>0.661</td>
</tr>
</tbody>
</table>

Control group was patient with supraventricular tachycardia. RFCA, radiofrequency catheter ablation; AF, atrial fibrillation; CK-MB, creatine kinase-MB; DM, diabetes mellitus; HDLC, high density lipoprotein-cholesterol; hs-CRP, high sensitive C-reactive protein; HTN, hypertension; IMR, index of microvascular resistance; LAD, left atrial dimension; LAV, left atrial volume; LDLc, low density lipoprotein-cholesterol; LVEF, left ventricle ejection fraction; LVIDd, diastolic left ventricular internal dimension; LVIDs, systolic left ventricular internal dimension; PeAF, persistent atrial fibrillation; T-Chol, total cholesterol. Triglyceride was expressed as median (25th, 75th percentiles range). P Value† were calculated using Fisher’s exact test. P Value‡ were calculated using Mann-Whitney U-test.
### Table 2. Cardiac Enzymes, Biomarkers, and IMR Before and After RFCA for Controls and AF Patients

<table>
<thead>
<tr>
<th></th>
<th>Control (n=34)</th>
<th>AF (n=49)</th>
<th>P Value</th>
<th>Control (n=25)</th>
<th>AF (n=24)</th>
<th>P Value</th>
<th>Control (n=13)</th>
<th>AF (n=36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before RFCA</strong></td>
<td></td>
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<tr>
<td>IMR (mmHg/s)</td>
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</tr>
<tr>
<td>hs-CRP (mg/l)</td>
<td>0.85 (0.15, 2.78)</td>
<td>0.64 (0.38, 1.03)</td>
<td>0.740(^\d)</td>
<td>0.62 (0.34, 0.95)</td>
<td>0.71 (0.45, 1.24)</td>
<td>0.635(^\d)</td>
<td>0.61 (0.34, 1.19)</td>
<td>0.64 (0.39, 1.03)</td>
<td>0.924(^\d)</td>
</tr>
<tr>
<td>NO (μmol/l)</td>
<td>93.96 ± 32.26</td>
<td>90.97 ± 31.14</td>
<td>0.608</td>
<td>87.24 ± 31.52</td>
<td>94.85 ± 30.91</td>
<td>0.398</td>
<td>107.59 ± 41.79</td>
<td>84.96 ± 24.31</td>
<td>0.141</td>
</tr>
<tr>
<td>ALCAM (ng/ml)</td>
<td>0.59 ± 0.53</td>
<td>2.25 ± 0.92</td>
<td>&lt;0.001</td>
<td>2.35 ± 0.80</td>
<td>2.14 ± 1.03</td>
<td>0.425</td>
<td>2.28 ± 0.84</td>
<td>2.23 ± 0.95</td>
<td>0.684</td>
</tr>
<tr>
<td>LpPLA2 (ng/ml)</td>
<td>297.28 ± 63.27</td>
<td>281.07 ± 93.66</td>
<td>0.259</td>
<td>301.65 ± 107.22</td>
<td>259.64 ± 73.28</td>
<td>0.117</td>
<td>296.42 ± 97.79</td>
<td>275.53 ± 92.91</td>
<td>0.441</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>59.78 (35.47,130.2)</td>
<td>220.2 (160.2,311.2)</td>
<td>&lt;0.001(^\d)</td>
<td>220.2 (161.7,314.9)</td>
<td>210.5 (134.5,311.9)</td>
<td>0.749(^\d)</td>
<td>259.2 (189.2,335.35)</td>
<td>185.6 (142.6,286.9)</td>
<td>0.298(^\d)</td>
</tr>
<tr>
<td><strong>After RFCA</strong></td>
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<tr>
<td>IMR (mmHg/s)</td>
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</tr>
<tr>
<td>hs-CRP (mg/l)</td>
<td>1.05 (0.46, 4.16)</td>
<td>15.04 (11.19, 21.32)</td>
<td>&lt;0.001(^\d)</td>
<td>13.56 (10.96, 21.13)</td>
<td>15.79 (11.23, 22.6)</td>
<td>0.624(^\d)</td>
<td>20.63 (5.9, 25.9)</td>
<td>14.53 (11.89, 17.11)</td>
<td>0.651(^\d)</td>
</tr>
<tr>
<td>NO (μmol/l)</td>
<td>94.65 ± 34.35</td>
<td>78.45 ± 27.23</td>
<td>0.021</td>
<td>72.21 ± 9.18</td>
<td>84.22 ± 29.89</td>
<td>0.148</td>
<td>92.62 ± 33.39</td>
<td>73.34 ± 23.09</td>
<td>0.046</td>
</tr>
<tr>
<td>ALCAM (ng/ml)</td>
<td>0.57 ± 0.50</td>
<td>2.49 ± 1.14</td>
<td>&lt;0.001</td>
<td>2.67 ± 1.23</td>
<td>2.31 ± 1.03</td>
<td>0.279</td>
<td>1.93 ± 0.92</td>
<td>2.69 ± 1.16</td>
<td>0.028</td>
</tr>
<tr>
<td>LpPLA2 (ng/ml)</td>
<td>291.49 ± 65.94</td>
<td>296.09 ± 96.43</td>
<td>0.953</td>
<td>316.30 ± 105.10</td>
<td>275.05 ± 83.51</td>
<td>0.136</td>
<td>274.62 ± 94.61</td>
<td>303.85 ± 97.21</td>
<td>0.602</td>
</tr>
<tr>
<td>CK-MB (ng/ml)</td>
<td>13.06 ± 5.52</td>
<td>12.17 ± 5.62</td>
<td>0.063</td>
<td>15.09 ± 5.13</td>
<td>14.01 ± 5.65</td>
<td>0.399</td>
<td>12.48 ± 5.23</td>
<td>14.01 ± 5.65</td>
<td>0.399</td>
</tr>
<tr>
<td>Troponin-T (ng/ml)</td>
<td>4.55 ± 1.05</td>
<td>3.84 ± 8.61</td>
<td>0.637</td>
<td>5.29 ± 12.45</td>
<td>4.08 ± 10.24</td>
<td>0.336</td>
<td>5.85 ± 11.80</td>
<td>4.08 ± 10.24</td>
<td>0.336</td>
</tr>
<tr>
<td>Myoglobin (ng/ml)</td>
<td>122.66 ± 154.90</td>
<td>93.92 ± 76.17</td>
<td>0.188</td>
<td>152.6 ± 205.40</td>
<td>141.35 ± 176.52</td>
<td>0.065</td>
<td>70.90 ± 33.84</td>
<td>141.35 ± 176.52</td>
<td>0.065</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>59.96 (40.26, 128.4)</td>
<td>117.9 (62.40, 354.7)</td>
<td>0.030(^\d)</td>
<td>96.34 (50.17, 155.6)</td>
<td>217.4 (79.4, 492.9)</td>
<td>0.101(^\d)</td>
<td>117.9 (73.18, 512.7)</td>
<td>123.4 (56.59, 285.2)</td>
<td>0.551(^\d)</td>
</tr>
<tr>
<td>Change in IMR</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Change in hs-CRP</td>
<td>0.01 (-0.19, 0.28)</td>
<td>14.13 (9.69, 19.35)</td>
<td>&lt;0.001(^\d)</td>
<td>12.75 (9.45, 17.52)</td>
<td>15.29 (11.16, 22.18)</td>
<td>0.307(^\d)</td>
<td>16.41 (5.70, 23.73)</td>
<td>14.01 (10.78, 16.45)</td>
<td>0.868(^\d)</td>
</tr>
<tr>
<td>Change in NO</td>
<td>0.69 ± 22.89</td>
<td>-12.51 ± 15.84</td>
<td>0.007</td>
<td>14.32 ± 21.06</td>
<td>10.63 ± 7.37</td>
<td>0.42</td>
<td>-14.97 ± 26.20</td>
<td>-11.63 ± 10.30</td>
<td>0.651</td>
</tr>
<tr>
<td>Change in ALCAM</td>
<td>-0.02 ± 0.26</td>
<td>0.25 ± 0.62</td>
<td>0.002</td>
<td>0.32 ± 1.37</td>
<td>0.17 ± 0.91</td>
<td>0.666</td>
<td>-0.35 ± 0.60</td>
<td>0.46 ± 0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in LpPLA2</td>
<td>-5.79 ± 30.69</td>
<td>15.02 ± 37.44</td>
<td>0.001</td>
<td>14.65 ± 33.48</td>
<td>15.41 ± 41.90</td>
<td>0.945</td>
<td>-21.80 ± 43.48</td>
<td>28.31 ± 24.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in BNP</td>
<td>3.93 (-3.10, 8.15)</td>
<td>-28.05 (-145.2, 174.2)</td>
<td>0.404(^\d)</td>
<td>-96.60 (-184.9, -2.46)</td>
<td>54.2 (-90.6, 216.2)</td>
<td>0.053(^\d)</td>
<td>-48.27 (-181.1, 214.8)</td>
<td>-28.05 (-145.2, 119.5)</td>
<td>0.981(^\d)</td>
</tr>
</tbody>
</table>

Control group was patient with supraventricular tachycardia. IMR, index of microvascular resistance; RFCA, radiofrequency catheter ablation; AF, atrial fibrillation; PAF, paroxysmal AF; PeAF, persistent AF; hs-CRP, high sensitivity C-reactive protein; NO, nitric oxide; ALCAM, activated leukocyte cell adhesion molecule; LpPLA2, lipoprotein-associated phospholipase; BNP, B-type Natriuretic Peptide; CK-MB, creatine kinase-MB.

\(^\d\)Values shown are differences between before and after RFCA. Hs-CRP and BNP were expressed as median (25th, 75th percentiles range). P Value\(^\d\) were calculated using Mann-Whitney U-test.
Table 3. Binary Logistic Regression Analysis: Variables Related to an Increase in IMR after RFCA for AF

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th></th>
<th>Multivariate Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>LAV (ml)</td>
<td>1.032 (1.00-1.06)</td>
<td>0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E wave (cm/sec)</td>
<td>0.961 (0.92-1.01)</td>
<td>0.087</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoglobin (ng/ml)</td>
<td>1.015 (0.99-1.03)</td>
<td>0.074</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change* in ALCAM</td>
<td>21.67 (3.34-140.59)</td>
<td>0.001</td>
<td>17.78 (2.05-153.90)</td>
<td>0.009</td>
</tr>
<tr>
<td>Change* in LpPLA2</td>
<td>1.054 (1.02-1.09)</td>
<td>0.001</td>
<td>1.06 (1.01-1.11)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; IMR, index of microvascular resistance; RFCA, radiofrequency catheter ablation; AF, atrial fibrillation; LAV, left atrial volume; ALCAM, activated leukocyte cell adhesion molecule; LpPLA2, lipoprotein-associated phospholipase.

*Values shown are differences between before and after RFCA.

Table 4. Predictors for Early Recurrence Following AF Ablation in Univariate and Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>No recurrence</th>
<th>Early recurrence</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=35)</td>
<td>(n=14)</td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>PeAF (%)</td>
<td>13 (37.1)</td>
<td>11 (78.6)</td>
<td>0.012</td>
<td>0.033</td>
</tr>
<tr>
<td>LAV (ml)</td>
<td>64.55 ± 26.18</td>
<td>85.43 ± 29.31</td>
<td>0.042</td>
<td>0.035</td>
</tr>
<tr>
<td>Ablation time (min)</td>
<td>104 ± 38</td>
<td>134 ± 38</td>
<td>0.025</td>
<td>0.475</td>
</tr>
<tr>
<td>Total procedure time (min)</td>
<td>134 ± 38</td>
<td>169 ± 59</td>
<td>0.015</td>
<td>0.402</td>
</tr>
<tr>
<td>CK-MB (ng/ml)</td>
<td>13.56 ± 5.88</td>
<td>13.73 ± 4.75</td>
<td>0.674</td>
<td>0.408</td>
</tr>
<tr>
<td>Troponin-T (ng/ml)</td>
<td>3.79 ± 7.26</td>
<td>6.45 ± 16.43</td>
<td>0.232</td>
<td>0.873</td>
</tr>
<tr>
<td>Myoglobin (ng/ml)</td>
<td>112.38 ± 174.50</td>
<td>148.36 ± 89.26</td>
<td>0.019</td>
<td>0.421</td>
</tr>
<tr>
<td>E wave (cm/sec)</td>
<td>76.60 ±15.68</td>
<td>77.14 ± 13.91</td>
<td>0.859</td>
<td>0.669</td>
</tr>
<tr>
<td>Change* in IMR (mmHg/s)</td>
<td>0.44 ± 11.47</td>
<td>9.29 ± 7.92</td>
<td>0.011</td>
<td>0.031</td>
</tr>
</tbody>
</table>

PeAF, persistent atrial fibrillation; LAV, left atrial volume; CK-MB, creatine kinase-MB; IMR, index of microvascular resistance.

*Values shown are differences between before and after RFCA.
Figure Legends:

**Figure 1.** Differences in IMR values before and after RFCA for AF. **A,** no recurrence group. **B,** recurrence group. IMR, index of microvascular resistance; RFCA, radiofrequency catheter ablation; AF, atrial fibrillation.

**Figure 2.** Differences in NO (A), ALCAM (B) and LpPLA2 (C) values before and after RFCA for controls and AF. **Left,** control group. **Middle,** AF with no recurrence. **Right,** AF with recurrence. Control group was patient with supraventricular tachycardia. IMR, index of microvascular resistance; NO, nitric oxide; ALCAM, activated leukocyte cell adhesion molecule; LpPLA2, lipoprotein-associated phospholipase; RFCA, radiofrequency catheter ablation; AF, atrial fibrillation.

**Figure 3.** Changes in the E/E’ ratio in subjects with (green line) or without (blue line) increasing IMR from baseline at one day, 1 month, and 3 months after RFCA. IMR, index of microvascular resistance; RFCA, radiofrequency catheter ablation.

**Figure 4.** Receiver-operator characteristic curves for the change in IMR were used to identify subjects with early recurrence during the first 3 months after RFCA. IMR, index of microvascular resistance; RFCA, radiofrequency catheter ablation.
**Recurrence (-)**

- **Pre-RFCA:** 21.9 ± 12.7
- **Post-RFCA:** 21.9 ± 10.6

\[ p = 0.231 \]

**Recurrence (+)**

- **Pre-RFCA:** 16.6 ± 10.5
- **Post-RFCA:** 26.9 ± 13.3

\[ p < 0.001 \]
AUC = 0.698
95% CI = 0.539-0.857
P = 0.028
Effects of Iatrogenic Myocardial Injury on Coronary Microvascular Function in Patients Undergoing Radiofrequency Catheter Ablation of Atrial Fibrillation

Hong Euy Lim, Cheol Ung Choi, Jin Oh Na, Jong-Il Choi, Seong Hwan Kim, Jin Won Kim, Eung Ju Kim, Seong Woo Han, Sang Weon Park, Seung-Woon Rha, Chang Gyu Park, Hong-Seog Seo, Dong Joo Oh, Chun Hwang and Young-Hoon Kim

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