Acute and Chronic Effects of Epicardial Radiofrequency Applications Delivered on Epicardial Coronary Arteries

Juan F. Viles-Gonzalez, MD; Reynaldo de Castro Miranda, MD; Mauricio Scanavacca, MD; Eduardo Sosa, MD; Andre d’Avila, MD, PhD

Background—Epicardial coronary injury is by far the most feared complication of epicardial ablation. Little information is available regarding the chronic effects of delivering radiofrequency in the vicinity of large coronary vessels, and the long-term impact of this approach for mapping and ablation on epicardial vessel integrity is poorly understood. Therefore, the aim of this study was to characterize the acute and chronic histopathologic changes produced by in vivo epicardial pulses of radiofrequency ablation on coronary artery of porcine hearts.

Methods and Results—Seven pigs underwent a left thoracotomy. The catheter was sutured adjacent to the left anterior descending artery and left circumflex artery, and 20 pulses of radiofrequency energy were applied. Radiofrequency lesions located no more than 1 mm of the vessel were used for this analysis. Three animals were euthanized 20 days (acute phase) after the procedure and 4 animals after 70 days (chronic phase). The following parameters were obtained in each vessel analyzed: (1) internal and external perimeter; (2) vessel wall thickness; (3) tunica media thickness, and (4) tunica intima thickness. The presence of adipoce tissue around the coronary arteries, the distance between the artery and the epicardium, and the anatomic relationship of the artery with the coronary vein was also documented for each section. Sixteen of 20 (80%) sections analyzed, showed intimal thickening with a mean of 0.18±0.14 mm compared with 0.13±0.16 mm in the acute phase (P=0.331). The mean tunica media thickness was 0.25±0.10 mm in the chronic phase animals compared with 0.18±0.03 mm in the acute phase animals (P=0.021). A clear protective effect of pericardial fat and coronary veins was also present. A positive correlation between depth of radiofrequency lesion and the degree of vessel injury expressed as intimal and media thickening (P=0.001) was present. A negative correlation was identified (r=−0.83; P=0.002) between intimal thickening and distance between epicardium and coronary artery.

Conclusions—In this porcine model of in vivo epicardial radiofrequency ablation in proximity to coronary arteries leads to acute and chronic histopathologic changes characterized by tunica intima and media thickening, with replacement of smooth muscle cells with extracellular matrix, but no significant stenosis was observed up to 70 days after the ablation. The absence of acute coronary occlusion or injury does not preclude subsequent significant arterial damage, which frequently occurs when epicardial radiofrequency applications are delivered in close vicinity to the vessels. (Circ Arrhythm Electrophysiol. 2011;4:526-531.)

Key Words: epicardial ablation ■ vascular injury ■ coronary artery injury ■ VT ablation

Epicardial radiofrequency ablation has being widely used worldwide for the treatment of several tachyarrhythmias.1–3 Overall, epicardial ablation is a relatively safe procedure, but some important complications including procedure-related death have been recently reported.4,5 Along with inadvertent perforation of the right ventricle, the risk of epicardial coronary injury is by far the most feared complication of the procedure because epicardial ablation may be performed in close proximity to coronary arteries.5–7

Clinical Perspective on p 531

The incidence of coronary injuries during epicardial ablation procedures is low.3,4 This is somewhat surprising, given the close proximity of coronary arteries to common sites of ablation and may be due in part to underrecognition and underreporting. In animal models, the application of radiofrequency energy and/or cryothermia directly on a coronary artery frequently causes acute edema with wall thickening and luminal narrowing, which then resolves to some extent.9 Within days, several but not all acutely damaged arteries develop medial necrosis and loss of intimal and elastic tissue, with the subsequent development of severe intimal hyperplasia. It has been thought that the size of the artery might have a protective effect against acute vascular damage after epicardial radiofrequency ablation: The larger the artery, the less likely for the acute thermal damage to occur.9 However, little
information is available regarding the chronic effects of delivering radiofrequency in the vicinity of large coronary vessels, and the long-term impact of this approach on epicardial vessel integrity is poorly understood. Therefore, the aim of this study was to characterize the acute and chronic histopathologic changes produced by in vivo epicardial pulses of radiofrequency ablation on coronary artery of porcine hearts.

**Methods**

Seven swine with a median weight of 35 kg (range, 22 to 48 kg) were studied. Each animal was given an intravenous injection of 500 mg of thiopental and was then intubated. Three animals were euthanized 20 days (acute phase) after the procedure and 4 animals after 70 days (chronic phase). A left thoracotomy was performed under intravenous general anesthesia with a continuous infusion of 157 mg of fentanyl, 1000 mg of ketamine, and 30 mg of midazolam diluted in 500 mL of saline solution. By suturing the catheter to the parietal pericardium, the heart was exposed. The parietal pericardium was opened, and the left ventricular aspect of the beating heart was exposed. The pericardial pericardium was opened, and the anterior epicardial surface of the heart was widely exposed to allow suture of the ablation catheter adjacent (as close as possible) or perpendicular to the left anterior descending (LAD) coronary artery and left circumflex (LCX) artery. By suturing the catheter to the epicardial surface, maximal and sustained electrode to tissue contact was achieved (Figure 1).6

**Radiofrequency Applications**

An Atakr Radiofrequency Power Generator (Medtronic Inc, Minneapolis, MN) was used for radiofrequency energy delivery. All applications were delivered between the ablating electrode and a reference electrode of 110 cm², located at the animal’s lower back. Power, impedance, and thermocouple temperature were continuously monitored. Single applications were delivered controlled for a constant temperature of 70°C. Pulses were delivered for 60 seconds unless an impedance rise occurred first. Power delivery was controlled automatically with temperature feedback from thermocouples embedded in each electrode or at the catheter tip in the case of the standard 4-mm tip electrode ablation catheter.6

Single radiofrequency lesions were created during the experiments using a standard commercially available 7F, quadripolar, 110-cm-long, 4-mm-tip catheter with a 2 mm–5 mm–2 mm interelectrode distance and a thermocouple positioned at the tip. In all applications, the catheter was sutured adjacent to the LAD and LCX to ensure adequate contact throughout the 60-second application. Radiofrequency lesions located no more than 1 mm of the vessel were used to evaluate the effects of these applications on the blood vessel wall and lumen.6

**Histological Analysis**

Lesions on the epicardial surface were measured with a surgical ruler to quantify width and length. Sections from grossly detectable lesions were taken and fixed in 10% neutrally buffered formalin for 7 days. The tissue was dehydrated, embedded in paraffin, sectioned at a 5-mm thickness, and stained with hematoxylin and eosin, α-actin, and Masson trichrome. Vessel size was determined by measuring its internal and external perimeter. All coronary arteries within 1 mm of a radiofrequency lesion were selected for analysis. Radiofrequency lesions situated 1 mm from a coronary artery were analyzed for lesion diameter and depth. Microscopic measurements were performed using the Quantimet 5001 Image Processing and Analysis System (Leica Cambridge Ltd, Cambridge, England). The device is a video analyzer that generates an electronic signal proportional to the intensity of illumination that is digitized into pixels. Measured parameters are expressed in pixels, but the final result is expressed in absolute units (eg, 1 pixel=0.00 299 mm).6

The following parameters were obtained in each vessel analyzed: (1) internal and external perimeter; (2) vessel wall thickness; (3) tunica media thickness, and (4) tunica intima thickness. The presence of adipose tissue around the coronary arteries, the distance between the artery and the epicardium, as well as the anatomic relationship of the artery with the coronary vein was also documented for each section. The deep wall of the artery (protected from radiofrequency lesion) was used as control for normal tissue.6

**Statistical Analysis**

SAS software (Cary, NC) was used for all calculations. Data are expressed as mean±SD unless otherwise indicated. Pearson correlation coefficient analysis and linear regression analysis were used to detect any association between each analyzed variable and the severity of a vascular lesion. Significance between acute and chronic lesions was tested using a 1-way repeated-measures ANOVA for all normally distributed variables. For intimal thickness (the only variable without normal distribution), we averaged 5 sections from each lesion (dependent measurements) and used a nonparametric test to compare the variables (Mann-Whitney test). Results for intimal thickness are expressed as median (25th and 75th percentiles). A value of P≤0.05 was considered significant.

**Results**

None of the animals had acute myocardial infarction or evidence of coronary thrombosis. Of note, all the segments analyzed demonstrated intact endothelium. Significant stenosis of the vessel lumen, defined as >70%, was not present in any of the sections analyzed in the acute or chronic phase.

**Acute Phase**

Thirteen applications were delivered in the initial 3 animals, and 12 of them were available for histological analysis. The mean power of radiofrequency ablation in this group was 6.9±6.20 W, with a mean impedance of 82.7±9.20 Ohms. Analysis of the tunica intima showed that 26 of 32 sections (81.3%) had some degree of intimal alteration. Mean intimal thickness was 0.13±0.16 mm. Immunostaining with α-actin
revealed that intimal thickening was at the expense of smooth muscle cell hyperplasia. Staining with hematoxylin and eosin increase showed that extracellular matrix had increase in eosinophilic fibers and amorphous basophilic material probably representing proteoglycans (Figures 2 and 3). Ten of 32 (31.3%) sections presented disruption of the internal elastic lamina. The disruption of the internal elastic lamina was a very interesting and unexpected finding, but we do not know the clinical implications that this may have. It could be hypothesized that during the remodeling process the internal elastic lamina gets reconstituted, but our study does not provide any mechanistic insight in this regard. There was no evidence of fat deposition as shown by Sudan IV staining (Figure 3).

Thickening of the tunica media caused by increase in extracellular matrix, decrease in smooth muscle cells and eosinophilic fibers, and monocyte infiltration, particularly in those with internal elastic lamina disruption, was noticed. The mean tunica media thickness was 0.18±0.03 mm in the acute-phase animals and 0.25±0.10 mm in the chronic-phase animals (P=0.021) (Figure 2). The deep wall of the artery was used for comparison among abnormal and normal tissue.

**Chronic Phase**

All 20 applications were available for histological analysis (5 per animal). The mean power of radiofrequency ablation in this group was 4.15±2.32 W, with a mean impedance of 89.55±14.85 Ohms. A trend toward more powerful radiofrequency pulses could be seen during the acute experiments, but it was not statistically significant (P=0.108). Sixteen of 20 (80%) sections analyzed showed intimal thickening with a mean of 0.20 mm (0.06 to 0.34 mm) compared with 0.18 mm

![Figure 2. Acute and chronic effect of radiofrequency lesion on coronary arteries.](image1)

**Figure 2.** Acute and chronic effect of radiofrequency lesion on coronary arteries. **A,** Acute effect of radiofrequency ablation on the left anterior descending coronary artery with significant intimal thickening. **B,** Chronic effect of radiofrequency application on the left circumflex artery characterized by intimal hyperplasia and internal elastic lamina disruption.

![Figure 3. Chronic radiofrequency lesion on the left anterior descending coronary artery: Histological characterization.](image2)

**Figure 3.** Chronic radiofrequency lesion on the left anterior descending coronary artery: Histological characterization. **A,** Chronic effects of radiofrequency ablation on the left anterior descending coronary artery with significant intimal thickening. **B,** **C,** and **D,** Magnification ×40 view of the section in **A,** **B,** Conventional hematoxylin and eosin staining; **C,** α-actin immunostaining for smooth muscle cells; and **D,** Sudan IV staining for adipose tissue.
Impedance RF lesion, expressed as medial (25th and 75th percentiles). Mean external perimeter, mm
Mean internal perimeter, mm
Media thickness, mm
Intimal thickness, mm
Power RF lesion, W

Table. Comparison Between Acute and Chronic Lesions

<table>
<thead>
<tr>
<th></th>
<th>Acute Lesion</th>
<th>Chronic Lesion</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power RF lesion, W</td>
<td>6.9±6.20</td>
<td>4.15±3.32</td>
<td>0.108</td>
</tr>
<tr>
<td>Impedance RF lesion, Ohms</td>
<td>82.7±9.20</td>
<td>89.55±14.85</td>
<td>0.497</td>
</tr>
<tr>
<td>Intimal thickness, mm</td>
<td>0.18 (0.02–0.34)*</td>
<td>0.20 (0.06–0.34)*</td>
<td>0.331</td>
</tr>
<tr>
<td>Media thickness, mm</td>
<td>0.18±0.03</td>
<td>0.25±0.10</td>
<td>0.021</td>
</tr>
<tr>
<td>Mean internal perimeter, mm</td>
<td>6.35±2.05</td>
<td>7.98±1.68</td>
<td>0.041</td>
</tr>
<tr>
<td>Mean external perimeter, mm</td>
<td>7.40±1.95</td>
<td>8.92±1.67</td>
<td>0.061</td>
</tr>
</tbody>
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Values are expressed as mean±SD, except for intimal thickness,* which is expressed as medial (25th and 75th percentiles).

(0.02 to 0.34 mm) in the acute phase (P=0.331). The mean tunica media thickness was 0.25±0.10 mm in the chronic-phase animals compared with 0.18±0.03 mm in the acute-phase animals (P=0.021). Examination of the tunica media revealed thickening caused by increase in extracellular matrix (Figure 2 and 3). A summary of the comparison between acute and chronic lesions is presented in the Table.

The mean internal perimeter was significantly smaller in the acute-phase group as compared with chronic-phase animals (6.35±2.05 mm and 7.98±1.68 mm, respectively P=0.041). There was a trend toward larger mean external perimeter of in the chronic-phase animals as compared with the acute-phase group (7.4±1.95 mm and 8.92±1.67 mm, respectively (P=0.061). This could be explained by the larger size of the animals during the chronic phase.

Predictors of Vessel Injury
Several variables were analyzed to assess their effect on vascular injury. The occurrence of intimal or media thickening was not associated with weight of the animal, power of radiofrequency ablation, impedance, internal or external vessel perimeter, thickness of the deep wall (not affected by radiofrequency), or internal elastic lamina disruption on a univariate regression analysis. Because of the small sample size, we could not perform a multivariate analysis. Therefore, we cannot predict whether the analyzed variables are independent predictors of vessel injury.

A positive correlation between depth of radiofrequency lesion and the degree of vessel injury, expressed as intimal and media thickening (r=0.81, P=0.0017), was present. In addition, the degree of intimal thickening correlated closely with thickness of the media. Additionally, a clear protective effect of pericardial fat and coronary veins was also present (Figure 4). When the vein was interposed (anterior to the artery) between the epicardium and the artery, the mean intimal thickness was 0.019 mm (0.004 to 0.034 mm), compared with 0.25 mm (0.04 to 0.46 mm), when the vein was on a different location (P=0.039). Similarly, the presence of epicardial fat between the radiofrequency lesion and the coronary arteries resulted in intimal thickening of 0.029 mm (0.003 to 0.53 mm), whereas in its absence the mean thickness was 0.25 mm (0.03 to 0.48 mm, P=0.0331). A negative correlation was identified (r=-0.83; P=0.002) between intimal thickening and distance between epicardium and coronary artery.

There were a number of variables analyzed that showed no significant correlation with the degree of intimal and media thickness including power, impedance, type of coronary vessel (LAD versus LCx), internal and external perimeter, and lesion of the internal elastic lamina. We believe that given the small amount of power typically delivered during these experiments (up to 5 W for most radiofrequency ablation) and the limited variability, it would be difficult to show statistically significant associations in power, temperature, and impedance drop.

Discussion
Because of the initial description of its utility for the ablation of VT associated with Chagas disease, transthoracic epicardial catheter ablation is being used to ablate different forms of ventricular tachycardia, accessory pathways, and atrial fibril-
Although few complications have been reported, enthusiasm for this approach must be tempered by the potential adverse effects of radiofrequency energy when the application is delivered in the vicinity of a major epicardial coronary artery. There is a paucity of experimental animal data examining the quality chronic effects and safety of epicardial radiofrequency lesion on coronary arteries.

In the present study, a porcine model was used to (1) investigate the histological features of epicardial linear radiofrequency lesions on epicardial coronary arteries and (2) compare acute and chronic histopathologic changes on the vessel wall. The primary findings include (1) chronic lesions showed similar degrees of intimal thickening than acute lesion; (2) chronic lesions present more severe media thickening than acute lesion; and (3) both coronary veins and epicardial fat exert a protective effect on coronary arteries.

Previous Findings
Our group previously showed that the susceptibility of damage of coronary vessels is inversely proportional to vessel diameter for a given amount of power, in which it is hypothesized that larger vessels are protected due to increased blood flow. For coronary arteries within 1 mm of an ablation lesion, small vessels showed severe injury, the presence of thrombosis, and intimal hyperplasia. For larger coronary arteries, the main findings were replacement of the medial smooth muscle cells with extracellular matrix and neointimal hyperplasia or intravascular thrombosis. This axiom appears to be valid for radiofrequency applications when <10 W is delivered. Larger arteries are also prone to acute occlusion if higher power applications (such as those given with irrigated-tip catheters) are delivered in thevicinity of the vessels.

Regarding the effect of alternative sources of energy for epicardial ablation, epicardial cryoenergy is believed to result in less endothelial and cellular disruption than radiofrequency energy, but results are discordant. Our group reported before that in the hyperacute phase (<1 hour), no evidence of microscopic injury was found in animals that received linear cryolesions across the LAD coronary artery or focal cryolesions in the vicinity of epicardial coronary vessels. More severe neointimal proliferation was associated with at least some degree of medial scarring and adventitial collagenous proliferation. No evidence of obstructive lesions or destruction of the internal elastica was observed, except for 1 lesion in group 2 that showed nearly occlusive neointimal proliferation.

Present Findings
Our results are in line with previous reports regarding the type of histopathologic changes associated with vessel injury caused by radiofrequency ablation: intimal and medial thickening with replacement of smooth muscle cells with extracellular matrix, particularly in the tunica media. Interestingly, despite a profound inflammatory response and hyperplasia in both the intima and media, our analysis suggests that significant stenosis, atherosclerosis, or thrombosis are not part of the natural history of these lesions.

An important observation was the protective effect that epicardial fat and coronary veins had on vessel injury. This underscores the importance of identifying both structures and understanding their anatomic relationship with coronary arteries before and during epicardial mapping and ablation. Currently there is no accepted strategy for this purpose. Additionally, it has been suggested that ablation from epicardial veins would be feasible, but our results indicate that ablating in close proximity to the epicardial coronary arteries without venous structure interposed could potentially lead to more severe vessel injuries.

Clinical Implications
Because of the lack of irrigation in the pericardial space and the use of nonirrigated catheters, radiofrequency applications were delivered at a very low power (4 to 8 W) in the present study. In contrast to our current clinical approach, the use of irrigated ablation catheters allows for much higher power to be delivered (up to 40 to 50 W). Therefore, arterial damage is expected to be even more important if higher power is used. Of note, we used a nonirrigated catheter; therefore we do not know whether irrigated catheters would create the same type of coronary lesions. Therefore, we believe that as a proof of concept, the nonirrigated catheter probably provides a realistic idea of how much vessel injury can be created with epicardial application of radiofrequency energy in close proximity to the epicardial vessels.

Although speculative, the possible protective role of fat and vein interposed between the ablation catheter and the coronary artery may be irrelevant when much higher-power settings are used, such as in clinical cases. It is also important to emphasize that severe lesions can occur even when an application does not result in acute occlusion of the epicardial vessel. Therefore, the only recommendation at this point is to evade the coronary arteries during epicardial catheter ablation. According the recent Heart Rhythm Society guidelines, a minimal distance of 5 mm between the ablation catheter and the coronary vessel should be used.

Conclusion
In this porcine model of in vivo epicardial radiofrequency ablation in proximity to coronary arteries leads to acute and chronic histopathologic changes characterized by tunica intimai and media thickening, with replacement of smooth muscle cells with extracellular matrix, but no significant stenosis was observed up to 70 days after the ablation. The absence of acute coronary occlusion or injury does not preclude subsequent significant arterial damage, which frequently occurs when epicardial radiofrequency applications are delivered in close vicinity to the vessels.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

We studied in a porcine model the acute and chronic histopathologic changes of epicardial vessels to evaluate the potential risk of delivering radiofrequency atop or in the vicinity of coronary arteries. The main finding of our study suggest that significant arterial damage (defined as tunica intima and media thickening) can occur several months after epicardial ablation even in the absence of acute coronary occlusion. These results have significant implications for epicardial catheter ablation that delivering radiofrequency energy close to an epicardial vessel will result in different levels of vascular injury, ranging from acute occlusion to late intimal hyperplasia. Thus, the decision to deliver radiofrequency closer than 5 mm to the vessels should be based on the clinical need, which should be balanced with the risk of vascular injury.
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